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UNIVERSITY
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TORONTO
MEDICAL
JOURNAL

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MARCH 1966 VOL. XLIII NUMBER 5

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Established December 1923
An Undergraduate Publication

Volume XLIII
Number 5
March 1966

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SUBSCRIPTION RATES: $4.50 for one volume of five consecutive issues. Single copies, $1.00.

MANUSCRIPTS including references and footnotes should be typewritten double spaced on one side of the paper. Articles should not exceed 3,000 words. Canadian Press (American) spelling is to be used. References should be kept to a minimum, and should be cited numerically in order in which they appear in the text.

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FINAL COPY DATE is the 15th two months prior to issue. Mailing date is the 15th of the month of issue.

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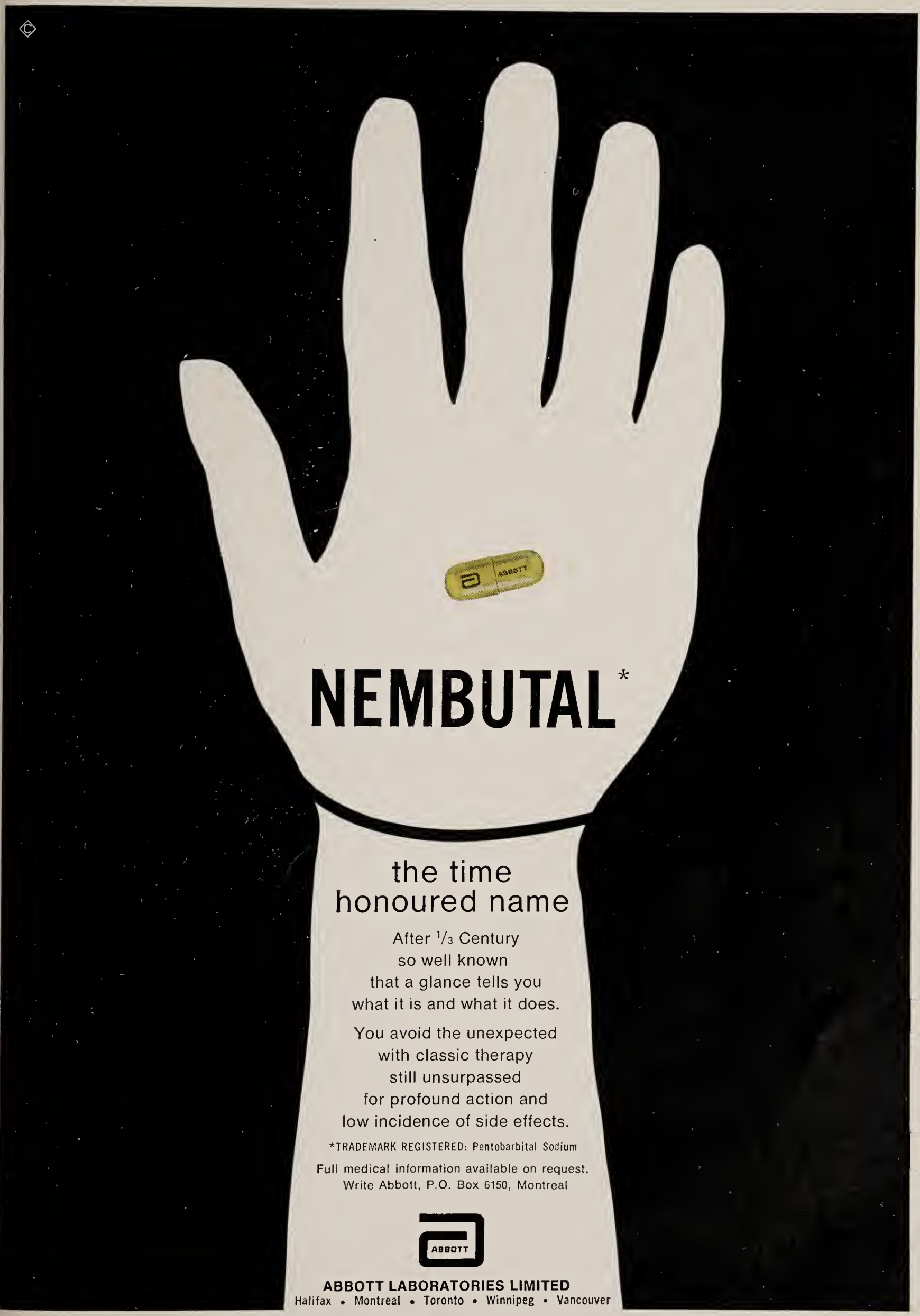

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Editorial

The last issue of Vol. XLIII deals in part with some interesting aspects of problematic disease entities of the gastrointestinal tract. The article on Hiatus Hernia and Reflux Esophagitis by W. J. Howes studies the incidence, the etiology, the radiological and esophagoscopic findings, the complications, and the treatment of hiatus hernia with reflux esophagitis. The wide variation in incidence of this condition points out the difficulties in assessing the role of etiological factors. The article on Chronic Active Hepatitis by D. P. Ballantyne reviews this disease entity of obscure etiology and pathogeneses. The role of emotional factors in ulcerative colitis is discussed by J. Richman in his article on Ulcerative Colitis and the Ileostomy Patient.

Diseases of the digestive tract have a long, often obscure history. Many well known diseases entities of today have their origin in antiquity. It was thought by the ancient Greeks that ascites was a manifestation of disease of the liver. Gallstones were also known by them to cause severe abdominal pain. Cardiospasm was well described by Thomas Willis in 1679 as a cause of vomiting. Jean Cruveilhier between 1829 - 1842 laid the foundation of much of our basic pathological and clinical knowledge about peptic ulcer. What appears from a study of history of medicine as singularly unique, is the relative poverty of knowledge both of yesteryears and even today about the aetiology of most diseases of the gastrointestinal tract. Although the pathogenesis of most diseases may been thoroughly studied, much knowledge is yet to be unravelled in order that we may discharge the yoke of theoretical considerations being accumulated in vast quantities. It may be considered as proof of fact that our knowledge about disease entities is inversely related to the number of theories of causation.

To bear fact, let's consider some statements Cruveilhier made about peptic ulcer. 'Anatomically considered, the simple chronic ulcer of the stomach consists of a spontaneous loss of substance, ordinarily circular, with the margins cut perpendicularly, the bottom gashed and thick and of variable dimensions. Almost always single, the ulcer is situated most commonly either on the small curvature or upon the posterior wall of the stomach. . . . Simple ulcer of the stomach does not present other than a gross resemblance to cancerous ulcer with which however, it has always been confused. . . . The history of the cause of the simple ulcer of the stomach is surrounded in profound obscurity. . . . The principle symptoms are the following: loss of appetite or bizarre appetite, insurmountable distress, difficult digestion, nausea or heavy pains in the epigastrium, and sometimes epigastric pain extremely sharp during the process of digestion or indeed when there is no food in the stomach. The epigastric pain, or rather the xyphoid or substernal pain, is referred sometimes to a corresponding place on the spine. . . . Pathological anatomy accounts fully for the bloody and black vomiting which often accompanies ulcer of the stomach.'

Since this classical description, much knowledge has accumulated elaborating in great length much of the Curveilhier's original description. However, in spite of such advances in our knowledge, the fundamental causative factors still elude us. Shay and Sun write in Bockus's book on Gastroenterology 'development of chronic peptic ulcer is determined by the algebraic sum of two groups of forces, acting upon the gastrointestinal mucosa, the one defensive and the other aggressive.'

Although a host of factors which contribute to the development of peptic ulceration have been revealed, the basic 'why' remains unanswered. What initiates the train of associated actions and reactions is unknown.

One of the fundamental difficulties in elucidating the aetiology of diseases of the gastrointestinal tract is the role of emotional factors in the pathogenesis. Are they primary, the trigger agent, or are they secondary colouring overtones?

A.G.L.

We have enjoyed having the opportunity of publishing medical articles which we feel are of interest to most medical students. We wish our best to the co-editors of Vol. XLIV, Terry Picton and Ken Pritzker. Many thanks to all who contributed their time in helping publish Volume XLIII.

A.G.L.

Hiatus Hernia And Reflux Esophagitis

W. J. Howes 6T6

In 1951 Allison[2] published an excellent description of the patient suffering from hiatus hernia with reflux esophagitis.

"A woman of 59 complains that for six years she has suffered from an intense burning pain behind the lower part of the sternum which rises up toward or even into the neck. The pain may spread into the jaw, the ear or the hard palate or radiate through to the back between the shoulder blades or down the arm. It comes on especially when she exerts herself stooping forward bending over the wash tub, poking the fire or fastening her shoes. It wakes her at night especially if she is sleeping on her back or her right side; and she seeks relief from what she describes as an agonizing pain by sitting upright and taking a few sips of water with an alkaline mixture. She says her throat usually feels dry and burning. When she swallows she may be conscious of the passage of food down the gullet; it may cause a feeling of soreness and may sometimes lodge behind the lower end of the sternum, causing pain which is immediately relieved as the bolus passes into the stomach. If she bends forward after a meal, food or some fluid rises into her throat and has to be swallowed again. Her husband says that for belching she takes first prize. Four years ago she was thought to have cholycystitis but removal of either a normal or abnormal gallbladder did not cure her. Roentgenography of her stomach and duodenum shows no evidence of ulcer. She has tried all the advertised stomach medicines with only temporary relief and has finally been told that "the nerves of her stomach have been upset by the change of life." "

Incidence

Incidence is difficult to assess as most studies are of patients with varied gastro-intestinal symptoms and are thus a select group. Reported frequency in these series ranges from 3.5% to 50%.

In a study of 300 symptom free men over 50 years of age an incidence of 1.3% was found.

Incidence also varies with the means used to demonstrate the hernia; Martin[21] found an incidence of 28% using a cushion to compress the abdomen, and of 11% without.

Etiology

Hiatus hernia is seen in the first year of life, and then not until middle age, with the peak incidence during the sixth decade. This is probably related to the increase in tissue laxity with age, and the length of time during which a hernia developes.

Approximately 60 to 70%[27 6] of hiatus hernia patients are females, perhaps as a late consequence of pregnancy. Pregnancy, obesity and other causes of increased intra- abdominal pressure are felt to contribute to the formation of hiatus hernias.

Anatomy

1. *Esophageal hiatus*[19]

The greater portion of the esophageal hiatus is formed by the right crus of the diaphragm with some contribution from the left crus in 50% of cases. The crura are joined in front of the aorta by the median arcuate ligament which also provides a point of origin for some of the hiatal fibres.

2. *Esopho-gastric junction*

The anatomy and terminology applied to the lower end of the esophagus is not standardized. Bochus[6] proposes the following nomenclature. The esophagus dilates into an *ampulla* proximal to the *inferior esophagal sphincter* which is seen radiologically, monometrically and by some at autopsy. The esophagus dilates below this into the *vestibule* which ends at the *constrictor of the cardia* forming the angle of His with the stomach. The vestibule may or may not be present, and usually contains the junction of gastric and esophageal mucosa. The crura of the diaphragm normally surround the vestibule, and are attached to it by the phrenico-esophageal ligament which arises from the fascia of the diaphragm and inserts into the serosa of the esophagus at the inferior esophagal sphincter above, and at the constrictor cardia below.

The point of where the stomach begins and esophagus ends is not settled, but for practical purposes it can be considered to be the angle of His,[10] as the site of junction of esophagal and gastric mucosa is so variable.

Sphincter Mechanisms

Gastric intraluminal pressure is greater than esophageal and thus were it not for some sphincter mechanisms at the esophago gastric junction, reflux would be common. The lower end of the diaphragm has been shown to be closed in the resting state at esophagoscopy and when viewed through a gastrostomy.

Among the mechanisms proposed are:

(1) *Diaphragm*

The diaphragm has been said to act as a pinchcock on the lower end of the esophagus and to protect this area from the pressure drop of inspiration.[2]

It's role is probably unimportant other than in maintaining anatomical relationships. Herniation occurs without reflux, and in dogs removal of the crus around the hiatus does not result in reflux.[26]

(2) *Sling fibres and oblique angle*

Willis called attention to a horseshoe shaped bundle of stomach muscle fibres running from the posterior, lateral to the cardia, and anterior on the stomach which he felt was important in maintaining the angle at the junction of the esophagus and stomach, the angle of His. This bundle has been described as uniting with the circular muscle surrounding the last centimetre of the esophagus.[20] The oblique angle of entry thus formed is said to prevent reflux by creating a flap valve of the gastric wall.

Smiddy and Atkinson[26] found that reducing the angle was the only factor affecting the yield pressure of the sphincter region. Gahagan[12] caused reflux esophagitis in dogs by dividing the sling fibres.

However, the angle of His at autopsy varies from 50 degrees to 170 degrees.[14] The importance of the fibres of Willis may be in contributing to the tone of the intrinsic sphincter.

(3) *Intra-abdominal segment of esophagus*

Creamer[9] suggests that the abdominal esophagus acts as a flaccid tube in the high pressure zone of the abdomen and collapses, particularily during inspiration and thus forms a valve; however reflux occurs in an abdominal esophagus when the intrinsic sphincter[20] is not present manometrically.

(4) *Mucosal rosette*

Botha[7] feels that prominent folds in the lining epithelium are important in preventing reflux. He had difficulty demonstrating these at autopsy, but felt they were palpable and had a positive tone at operation. They may be important in conjunction with the intrinsic sphincter although Allison[3] belittled their importance and stated that any mucosa lined muscular tube will show folds when contracted.

(5) *Intrinsic sphincter*

Fyke[11] and Atkinson[4,5] both reported a high pressure area at the lower end of the esophagus which relaxed as part of the swallowing reflex. By withdrawing manometric equipment through the esophago-gastric junction they demonstrated an area of high pressure averaging ten centrimetres of water above fundic pressure, which was one to four centimetres long and usually extended from two centimetres above to one centimetre below the diaphragm. The diaphragm was identified as the pont where the inspiratory swing of pressure changes from positive to negative. Atkinson also showed the same high pressure area in hiatus hernia without reflux and the absence of this high pressure area in hiatus hernia with reflux.

The anatomical basis of this area appears to be the lower esophageal narrowing found three to four centimetres above the sphincter of the cardia. First described by Laimer in 1883 it is now known as the inferior esophageal sphincter. Lerche[18] described a thickened area of muscle at this site in 60 of 80 cadavers but most anatomists have not found this; Peters[25] in 2000 dissections could not demonstrate it. In the bat there is a definite sphincter five to six times as thick as the rest of the stomach.[14]

The importance of the intrinsic sphincter in preventing reflux is shown by the presence of reflux without hiatus hernia.

The concept of a tonic sphincter has been questioned by Harris and Pope,[13] who studied the readily accessable rectal sphincter and found sphincter pressure measured by manometric equipment commonly in use correlated only to pressure which has been measured just previously in withdrawing the apparatus. They propose a sphincter mechanism which resists opening but is not tonicly active.

Types

The sliding hiatus hernia is characterized by transposition of the esophago-gastric junction to above the diaphragm. Ligamentous attachments are stretched, the hiatus enlarges, the peritoneum is drawn into the hiatus about the esophagus and the angle between stomach and esophagus becomes more obtuse.

The paraesophageal hernia is much less common and consists of a peritoneal sac which contains stomach and extends through the hiatus, while the posterior ligamentous attachments remain short and the esophago-gastric junction remains below the diaphragm.

Although congenital short esophagus is likely a true entity, it is a rare one. Humphrey described a case in which the thoracic stomach was supplied by aortic segmental vessels.[19] Most short esophagus is the result of fibrosis causing a sliding hernia to become irreducable.

Radiology

Hiatus hernia is demonstrated by barium swallow with the patient in the Trendelenburg position. A cushion may be used to compress the abdomen. Gastric mucosa above the diaphragm and widening of the hiatus are diagnostic signs of importance. Schatzki's ring, a narrowing at lower end of the esophagus is considered by some to indicate hiatus hernia. This narrowing may

represent the result of fibrosis or may be a prominence of the inferior esophageal sphincter caused by the relative shortening of the muscularis as compared to the mucosa with mucosal out-pouching. It can cause dysphagia. Reflux itself is not always diagnostic; and most consider the presence of the vestibule above the diaphragm as normal.

Esophagitis may be seen as an area of esophagus lacking distensibility or actually narrowed. The mucosa may appear smooth or irregular.

Esophagoscopy

Esophagoscopy is useful in localising the mucosal junction in relation to the diaphragm, and is useful in eliminating the possibility of carcinoma. Esophagitis appears as hyperemic, edematous mucosal folds, friable congested areas, or areas of ulceration or erosion which may be covered with a shaggy pseudo-membrane.

Associated Conditions

The high association of hiatus hernia, gallbladder disease and colonic diverticula is known as Saint's triad; gallbladder disease is reported in 14 to 26% of patients with hiatus hernia.[17] A high association of duodental ulcer and symptomatic hiatus hernia is also reported.

Complications

The majority of hiatus hernias are probably without complications.

Bleeding

Bleeding has been reported in 27% of 138[15] and in 30% of 500[17] adult hiatus hernia patients, but only in 13% of the 500 was the bleeding due to reflux esophagitis, esophageal ulceration or ulceration of the gastric pouch. However gastritis which may result from stasis in the gastric pouch is difficult to diagnose.

Reflux esophagitis

Although reflux esophagitis can occur secondarily to other causes; prolonged vomiting, pregnancy, obstructing duodenal ulcer, scleroderma and Heller's procedure, Ellis[10] in a summary of other reports found that 76% of reflux esophagitis was secondary to hiatus hernia. Many of those with hiatus hernia have a peptic ulcer, a history of peptic ulcer or a high gastric acid secretatory pattern. Casten[8] found the presence of a high overnight secretion rate in 84% of 105 symptomatic hiatus harnias and 32% of the 105 had a duodenal ulcer. Sweet[27] found only 28% with an ulcer or history suggestive of one. In dogs destruction of the sphincter causes esophagitis, repair arrests it. However Palmer[24] has described reflux esophagitis in a patient with histamine fast achlohydria.

Reflux esophagitis can be classified into three types. *Peptic esophagitis* is a superficial linear ulceration of the squamous epithelium occuring in the normally lined esophagus. It comprises about 25%[22] of reflux esophagitis. Stricture formation is rare in the absence of duodenal ulcer. *Marginal esophageal ulceration* occurs in squamous epithelium within two centimetres of the junction of gastric and esophageal mucosa, and is found only with hiatus hernia and short esophagus. It comprises 64% of esophagitis and has a definite tendency towards stricture formation. *Peptic ulcer of columnar epithelium*, comprising the remaining one per cent of esophagitis, is a deep circumscribed lesion at or near columnar epithelium which acts similarily to a gastric ulcer with a tendency to bleed and perforate. Also known as Barret's ulcer, it arises from columnar epithelium which may be primarily heterotropic, which has originated in the deep glands at the cardia or which has invaded upwards from the gastric epithelium during the healing stages of one of the previous forms of esophagitis.[1]

Short Esophagus

Shortening of the esophagitis is a term used to describe hiatus hernia in which the esophago-gastric junction lies above the diaphragm and cannot be reduced. It is a result of reflux esophagitis, mucosal fibrosis and hypertrophy of the muscularis resulting in contraction of the distal esophagus which may or may not be associated with stricture.

Stricture

Stricture is the result of fibrosis causing circumferential contraction, usually as a sequela of marginal ulceration, and may result in obstruction of the esophagus.

Others

Rarely the gastric pouch may become obstructed or strangulated, or if large may cause respiratory distress. Gastro-pleural fistulae have been described.[17]

An increased incidence of carcinoma of the esophagus has been reported,[28] denied by others, and is certainly an important differentiation to be made.

Treatment

The treatment of hiatus hernia is important if the complications of short esophagus and stricture are to be avoided.

In the absence of severe complications the primary treatment is non-surgical. Obesity must be treated vigously. The avoidance of tight abdominal garments, intensive antacid therapy combined with small frequent meals and no snacks three hours before bedtime are all important aspects of treatment. Sleeping in a sitting position may prove necessary. Anticholinergics, while diminishing the vagal phase of gastric secretion, also delay gastric emptying and may weaken the esophagogastric sphincter. Patients with a duodenal ulcer have a poorer prognosis on a medical regime and may require surgery earlier.

Surgery will be required in the ten to 15% of patients which (1) conservative measures are unsuccessful in controlling symptoms, (2) esophagitis or ulcers do not heal and the danger of stricture is high, or rarely (3) chronic bleeding leads to anemia. The aims of operation are to eliminate reflux or to minimize its effects, ideally by restoring the action of the esophago gastric junction.

An abdominal approach is preferable because of the high association with other intra-abdominal conditions, however a left thoracic approach may be necessary in the very obese, or in face of adhesions from other abdominal operations. The stomach is reduced into the abdomen and maintained by suturing the crus either posterior or anterior to the esophagus, and by repair of the phrenico-esophageal ligament. Fundoplication,[23] the folding of the fundus around the lower esophagus has been advocated to create a more acute angle, and to act as an artificial valve. Gastropexy,[23] reduction of the hernia by suturing the cardia to the diaphragm and anterior abdominal wall has been described as a successful procedure. Patients with a high acid secretion rate or duodenal ulcer should have in addition either a gastrectomy or vagotomy and pyloroplasty. In dogs a substitute sphincter formed from an innervated diaphragmatic muscle flap has been found to prevent reflux.

Short esophagus will prevent reduction of the hernia and measures to diminish the amount of gastric acid which refluxes into the esophagus will have to be taken. If the associated esophagitis is mild it can be treated with a vagotomy and pyloroplasty, if more severe a vagotomy and hemi-gastrectomy may be required.

Stricture should be treated with bougie dilitation if it is causing dysphagia, followed by vagotomy and pyloroplasty to minimize the effect of the reflux which will follow relief of the stricture. Severe stricture, often associated with short esophagus may necessitate resection of the stricture. The distal end of the esophagus may be reanastomosed to a tube formed from stomach, or a section of jejeunum or colon transplanted to replace that segment. Interposition of a segment of jejeunum, described by Merendino, is intended to resist reflux by peristaltic action.

Discussion

Both the sliding and the paraesophageal hiatus hernia seem to be the result of intra-abdominal pressure, often raised excessively by obesity pregnancy or constricting apparel, acting over long periods of time to stretch muscular and ligamentous structures which themselves have become less resistant to such stresses due to the effects of aging and hormone withdrawal. In the sliding hernia the attachments at the hiatus give way uniformly, however in the paraesophageal type of hernia the pressure acts on a localised weak or congenitally absent area of the supporting structures at the hiatus and the stomach and a peritoneal sac are pushed out of the abdomen at this point. With the formation of a paraesophageal hernia the hiatus will be even less able to resist pressure and the development of an additional sliding hernia is facilitated.

The mechanism principally responsible for the prevention of reflux would seem to be the intrinsic esophageal sphincter, with the diaghragm, the intra-abdominal position of the lower esophagus, the mucosal rosette, the angle of His, and the bundle of Willis all acting to give this shincter a mechanical advantage.

Herniation of the esophago-gastric junction results in loss of the mechanical advantage which the sphincter has had in its intra-abdominal position and it is not able to resist the reverse of gastric juice which occurs when one bends over or distends the stomach with a large meal. In fact in a sliding hernia the gastric contents are funnelled into the region of the sphincter by the shape of the herniated portion of stomach. With time the reflux of acid and digestive juices leads to esophagitis, further damaging the sphincter area.

Conservative treatment is aimed at preventing or ameliorating the damage caused by reflux which occurs, in the early stages, only with high gastric intra-luminal pressures. In the majority of persons these measures are sufficient to allow the intrinsic sphincter to function in its thoracic position.

In those whom irreversible damage has occured to the sphincter or in whom a high gastric acid secretatory pattern is found which continues to cause symptoms and damage in spite of conservative therapy, surgical therapy will be necessary. The esophago-gastric junction is returned to a position where (hopefully) it will function most effectively. If the sphincter cannot be salvaged procedures to diminish gastric acid and to enhance gastric emptying should be done to protect the esophagus from further damage.

Strictures which form at the esophago-gastric junction protect the esophagus from any reflux and in treating them measures must be taken to replace this natural protection by a gastric drainage procedure or an artificial sphincter mechanism.

ACKNOWLEDGEMENT

I wish to thank Dr. R. I. Mitchell for his suggestions, and for reading and criticising this paper.

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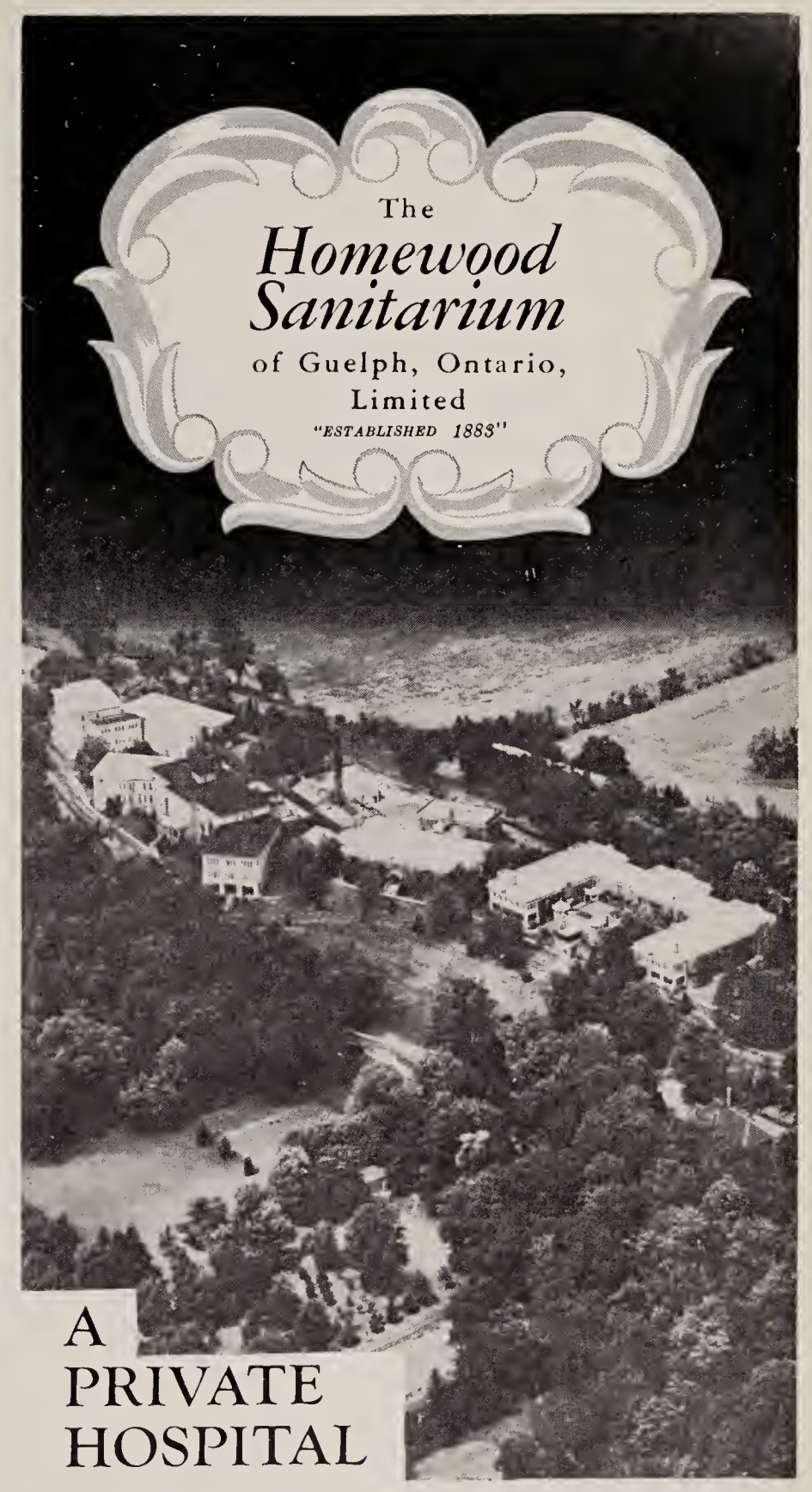

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Chronic Active Hepatitis

D. P. Ballantyne 6T6

Chronic active hepatitis is a disease entity which has been given a number of other designations, such as chronic liver disease in young women, active chronic viral hepatitis, cryptogenic cirrhosis, subacute hepatic necrosis, plasma cell hepatitis, active "juvenile" cirrhosis, and lupoid hepatitis. Chronic active hepatitis is a disease which occurs predominately in young women, and is manifested by: 1) progressive hepatic involvement with jaundice and other evidence of hepatocellular damage; 2) serological and protein abnormalities with hypergammaglobulinemia, serum antinuclear factors and often L. E. cells; and 3) evidence of systemic involvement with a variety of symptoms including skin rashes, arthralgias and arthritis. Liver histology reveals hepatocellular necrosis, fibrosis, and infiltrates of lymphocytes and plasma cells. These patients go through periods of remission and relapse, but generally follow a downhill course to death from liver failure and postnecrotic cirrhosis within ten years.

Incidence[5 6 18 21]

The patient most often affected by chronic active hepatitis is a young, healthy female in her teens or early twenties. However, the disease may occur at any age, and may rarely involve males. There is no racial or ethnic predominance.

Presentation[5 6 16 18 23]

Patients most commonly present with the insidious development of unexplained fatigue and jaundice.[18] In other instances, patients may first complain of arthritis, pleurisy, unexplained amenorrhea, skin rashes, or recurrent bouts of fever and abdominal pain. These multisystemic complaints often precede clinical evidence of liver disease by many months or years.[5 6 16 18 23]

In about one third of cases, the onset is acute, with fever, anorexia, jaundice and an enlarged tender liver suggestive of acute viral hepatits. This acute attack subsides, but the remission is incomplete with the result that the hepatitis smolders on as chronic active hepatitis.

Course and Clinical Picture[4 5 6 16 18 21]

The course of chronic active hepatitis is characterized by remissions and relapses of active liver disease leading inevitably to severe liver failure and postnecrotic cirrhosis. Death usually occurs within ten years[6] of onset, from massive hemorrhage of esophageal varices, progressive hepatic coma and intractable ascites. The terminal event is often precipitated by an intercurrent bacterial infection.

The clinical manifestations are best viewed in two groups; those findings directly related to the liver disease, and those systemic manifestations not attributable to the liver disease.

With the clinical onset of the hepatitis or during a relapse, the patient becomes febrile, jaundiced, weak, and fatigues easily. Manifestations of liver disease which appear early, are hepatomegaly (95%), spider nevi, palmar erythema and gynecomastia in males. Clubbing is rare. If the disease process is more advanced, there may be signs of overt fluid retention in the form of ascites and peripheral edema, transient episodes of hepatic coma, recurrent bacterial infections, and bleeding from esophageal varices.

Besides the manifestations of hepatic dysfunction, there are almost always manifestations of systemic involvement which cannot be directly related to the liver disease. These generalized complaints may precede evidence of hepatic involvement by many years,[3 5 6] the chronic liver disease being discovered only incidentally, or these systemic complaints may occur during periods of active liver destruction and evidence of hepatic dysfunction. The severity of the systemic manifestations tends to parallel the course of the liver disease, being most pronounced during exacerbations of fever and increasing jaundice. In most cases these systemic manifestations ressemble systemic lupus erythematosus.[5 14 15]

Rheumatic complaints, which are migratory in some instances, occur in 40 - 80% of cases, although objective evidence of joint involvement (arthritis) occurs in only 15 - 50% of cases.[6 14 18] The wrists and ankles are most frequently involved, but involvement of the shoulders, knees, proximal interphalangeal and metacarpophalangeal joints is common. The joints are painful and swollen, resultant deformities do not occur, and there is no X-ray evidence of bony erosion.[18] Subcutaneous rheumatic nodules have not been seen by most authors, although Bearn et al[6] reported two such cases.

Splenomegaly occurs in about 75% of cases and generalized lymphodenopathy in 15% of cases.[18] The splenomegaly often occurs before portal hypertension is present, and is usually asymptomatic, although rarely there are complaints of a dragging sensation or pain in the abdomen.[6]

The skin is frequently involved with various types of rashes,[18] and Mackay[14] has described two patients with the typical facial rash of S.L.E. Another feature common to these patients is unusually sensitivity to sunlight and drugs, resulting in a vesicular skin eruption. Endo-

crine disturbances are common, with delayed onset of menstruation or amenorrhea frequently being the presenting complaint. Genital hypoplasia, infertility and abdominal striae also occur.

Anemia, leukopenia and thrombocytopenia are common findings. The anemia is usually of moderate degree, normochromic and Coomb's negative. It is most probably due to hypersplenism, as splenectomy gives amelioration of the anemia as well as the leukopenia and thrombocytopenia.[18]

Other less frequent systemic manifestations associated with chronic active hepatitis are ulcerative colitis, pleurisy, myocarditis, pericardiatis, renal involvement, acute rheumatic fever, chronic rheumatic heart disease, rheumatoid arthritis, systemic sclerosis, Sjögren's syndrome, Hashimoto's disease and Raynaud's phenomena. Neurological manifestations are rare but grand mal convulsions, subarachnoid hemorrhage, epilepsy, hemiplegia, psychosis and polyneuropathy have all been described.[19]

Biochemistry and Liver Function Studies[5 14 15 18]

Serum bilirubin, SGOT, the sedimentation rate and serum levels of vitamin B_{12} are all elevated. Serum alkaline phosphatase is moderately elevated in all cases, but late in the diseases it is often raised to levels usually associated with obstruction. The prothrombin concentration is usually less than 60% and shows a poor response to vitamin K. The retention of BSP at 45 minutes varies from 14 - 44% and the total cholesterol is usually decreased.[18]

In general, the degree of abnormality seen in the liver function studies correlates well with the activity of parenchymal damage as determined by liver biopsy. During exacerbations of the hepatitis, the bilirubin and SGOT rise to high levels, and during remissions, return towards normal. However, near normal values for liver function studies may occur in the face of histological evidence of severe hepatitis and early cirrhosis.[18] The reverse is rarely true.

Serum Proteins and Serological Abnormalities

The most constant abnormality seen in chronic active hepatitis is the marked degree of hypergammaglobulinemia which may reach levels of 8 grams %.[16 18] Electrophoresis of the serum proteins shows a striking broad-based elevation of the gamma globulin to levels rarely seen even in those diseases marked by hypergammaglobulinemia, a decrease in albumen and frequently decreased beta and alpha globulins. The serum albumen is only slightly reduced until late in the disease when it may fall to extremely low levels. During clinical remission and return of liver function towards normal, the level of gamma globulin tends to decrease while the albumen rises.

The serological changes frequently seen in chronic active hepatitis are a positive latex agglutination reaction, a positive serum antinuclear factor reaction, a positive L.E. cell phenomena, positive autoimmune complement fixation tests (AICF test) and a false positive serological test for syphilis. The exact significance, if any, of these findings remains uncertain. Are the serological abnormalities related to the severity and clinical course of the disease? Do these findings indicate an abnormal immune mechanism, and are any of these findings specific for chronic active hepatitis?

The latex agglutination reaction is frequently positive in chronic active hepatitis, as well as in 25 - 60% of patients with acute viral hepatitis and various other forms of chronic liver disease.[18] There seems to be no correlation between this reaction and either the presence or the severity of rheumatic complaints in these patients.

Circulating antinuclear factors (antibodies) have been demonstrated in the serum of patients with chronic active hepatitis, as well as in patients with other forms of chronic liver disease.[18] Titres of these factors in chronic active hepatitis tend to be low, and usually are found only during a relapse of the disease.[13] Serum antinuclear antibodies are invariably present in the presence of L. E. cells and often in the absence of L. E. cells.

The L.E. cell phenomena is positive in 16% to 75% of cases of chronic active hepatitis, the percentage often depending on the enthusiasm of the search.[15 18 24] This is remarkable, as the phenomena is rarely, if ever, seen in other forms of chronic liver disease. The L.E. cell reaction in chronic active hepatitis is usually only weakly positive, being found only during a relapse, especially early in the course of the disease, and disappearing during remissions.

The significance of the LE cell, or its absence, on the clinical course of the disease is disputable. Mackay[15] believes that chronic active hepatitis in which there is a positive L.E. cell (a condition he calls lupoid hepatitis) is associated with an increased incidence of systemic involvement. Other investigators[1 5 11] are in agreement with this and find that chronic active hepatitis with a positive L.E. cell usually follows a more rapidly downhill course. In contrast to these views, Maclachlin et al,[18] feel that the presence of an L.E. cell bears no relation to the multisystemic disease, and Homan and Tomasi,[9] have noted cases of chronic active hepatitis without a positive L.E. cell which are clinically indistinguishable from cases of chronic active hepatitis in which positive L.E. cells are found.

Positive L.E. cells have been found in a number of conditions besides S.L.E., such as rheumatoid arthritis, miliary tuberculosis, multiple myeloma, generalized moniliasis, pernicious anemia and following hydralazine administration. Homan and Tomasi[9] believe that

the L.E. cell is not specific for any disease, whereas others believe that it represents either underlying S.L.E. or a lupus diathesis.[5] Most investigators feel that the presence of L.E. cells in chronic active hepatitis is indicative of an abnormal immune mechanism.

Mackay[12 16] found that the autoimmune complement fixation test (A.I.C.F. test) was positive in about one-half of those with S.L.E., acute viral hepatitis, and lupoid hepatitis, but in those cases a chronic active hepatitis without an L.E. cell, only 13% had a positive A.I.C.F. test. However, the A.I.C.F. test appears to be entirely non-specific as the serum from patients with a wide range of diseases will fix complement when mixed with a wide variety of tissue homogenates. The titre level is not related to the clinical state,[13] and some investigators think it doubtful whether the A.I.C.F. test is even indicative of autoimmune disease.[18]

Biological false serological tests for syphilis occur in 20% to 40% of patients with chronic active hepatitis.[5 18]

In general, most of these serological abnormalities, with the exception of the L.E. cell reaction, seem to be rather non-specific for chronic active hepatitis and not related to the clinical course of the disease or the presence of systemic manifestations. The significance of the L.E. cell phenomena regarding progression of the disease, incidence of multisystemic involvement, underlying immunological disturbances and relation to S.L.E. remains uncertain.

Pathology[3 4 13 16 18 23]

The evolution of chronic active hepatitis is a histological continuum of persistent or recurrent liver cell necrosis, increasing fibrosis, and eventually postnecrotic cirrhosis. The active stage of the disease is characterized histologically by persistent degeneration and necrosis of liver cells, widespread collapse and "collagenization" of the supporting reticulin fibres, and some degree of infiltration by inflammatory cells.

Liver cell destruction is the most salient histological feature of the disease, and is evidenced by actual loss of liverplate segments with lobular disarray, the appearance of condensed acidophilic cells with pyknotic nuclei, assumed to represent dying liver cells, (called Councilman-like bodies) and the presence of distorted swollen liver cells containing bizarre, often multiple, nuclei. Fibrous replacement occurs subsequent to this loss of liver cells. The inflammatory infiltrate is composed mainly of lymphocytes and plasma cells, with fewer numbers of polymorphonuclear leukocytes and eosinophils. These infiltrates are found most often in the fibrosed areas, (much of which is collapsed reticulin) and may be so marked, that actual lymphoid follicles with germinal centers develop. This combination of parenchymal and mesenchymal change is practically diagnostic of the disease.[23]

Additional and less specific histological findings in the liver include regenerative activity of the surviving liver parenchyma resulting in pseudolobules of varying size, proliferation of biliary radicles and bile ducts, inconstant cholestasis and prominence of the Kupffer cells.

The continuing necrosis and fibrosis results in intrahepatic disorganization with sequestration of parenchymal-cell masses, loss of the normal vascular and bile duct relations, and eventually the malfunctioning liver of postnecrotic cirrhosis. At autopsy, the liver is greatly reduced in size, and presents a grossly irregular surface with projecting nodules and deep fibrous scars between.

The usual findings at autopsy are postnecrotic cirrhosis, splenomegaly and evidence of portal hypertension and chronic liver disease. In many cases, little else is found to suggest a systemic disorder. Bartholomew[4] and Baggenstoss[3] in a study of six cases of chronic active hepatitis coming to autopsy, reported finding fibrinous pleuritis in two cases, fibrinous pericarditis in two cases, and endothelial proliferation in the glomerular tufts of all six cases lesions which they considered to be consistent with S.L.E. However, they were not able to find any lesions which they considered pathonomonic of lupus such as hematoxylin bodies, wire-loop lesions in the glomeruli, or periarterial fibrosis in the spleen.

Etiology and Pathogenesis[5 6 9 11 18 19 23]

The etiology and pathogenesis of chronic active hepatitis is obscure, but most present day theories implicate either a viral or an autoimmune process, (including S.L.E.) or a combination of the two. In all probability, however, there is more than one cause for this same clinical entity, as most reports in the literature deal with groups of patients which are carefully selected in order to support either one theory of causation and pathogenesis or another.

Theory I

Tisdale[23] and Klatskin[11] suggest that chronic active hepatitis probably represents a grave variant of viral hepatitis and results from an acute or anicteric attack of hepatitis which persists because of poor host response or peculiar virulence of the virus. Tisdale[23] believes that the development of chronic active hepatitis from viral hepatitis is dependent on the age, sex, hormonal status and general resistance of the patient. The chronic activity of the diseases is due to the persistence of the viral infection, the mononuclear infiltrate is a host response to the continuing liver cell damage, and the serological and protein abnormalities reflect the presence of these mononuclear cell infiltrates. In this view, the serological abnormalities and L.E. cell phenomena are just coincidental and play no part in the pathogenesis of the disease, nor do they bear any relation to S.L.E. The systemic manifestations, if present, may be due to dissemination of the virus.

Bearn et al[6] suggested that the predominance in young women, and the adverse effects of estrogen administra-

tion on the course of the disease, may indicate that the endocrine changes in young women modify the usual course of the benign viral hepatitis.

Evidence in favour of a viral etiology is found in the liver biopsy which reveals a histological pattern indistinguishable from viral hepatitis.[11 13] There is often a history of contact with a jaundiced person, and a history consistent with viral hepatitis is obtained in 10% to 65% of cases.[3 18 23] However, the responsible virus has never been isolated and it is difficult to explain the systemic manifestations, especially if they precede the liver disease, on a viral basis.

Theory II

Mackay and associates[13 14 15] believe that chronic active hepatitis and its sequel postnecrotic cirrhosis, are the result of an immunological process occurring primarily in the liver, where the patient develops immune reactivity to his own liver cells. They believe that the initial damage to the liver may be a viral or nutritional injury, that allows liver cell components, which are normally not accessible to the lymphoid system, to become antigenic and provoke an autoimmune response. The liver is colonized by immunologically competent lymphoid cells which are responsible, not only for the protein and serological abnormalities, but through their pathogenic activity, are responsible for perpetuating the hepato-cellular damage.

These investigators have coined the term lupoid hepatitis to refer to chronic active hepatitis with a positive L.E. cell, and occasionally manifestations, usually minor, of S.L.E. Although Mackay differentiates lupoid hepatitis from S.L.E. on a clinico-pathological basis, he suggests that the overlapping features of the two may indicate a similar pathogenesis, and that the systemic manifestations of both conditions may be explained on an autoimmune basis.

Theory III & IV

The probability of chronic active hepatitis being related to S.L.E. depends on the group of patients studied, and whether or not the patients have a positive L.E. cell and evidence of a multi-systemic disease. Chronic active hepatitis may be related to S.L.E. in one of two ways. Chronic hepatitis may result from a coincidental attack of viral hepatitis in a person with underlying S.L.E., whose abnormal immune response is responsible for the serological abnormalities and the perpetuation of the hepatic inflammation. The systemic manifestations would then be attributed to S.L.E. The other possibility is that persistent active hepatitis may be an unusual, but major manifestation of S.L.E. in certain patients.

There is some evidence for the relationship of chronic active hepatitis to S.L.E. The systemic manifestations in both conditions often bear a close ressemblance, the systemic manifestations of chronic active hepatitis often precede the liver disease, and S.L.E. has been found in close relatives of patients with chronic active hepatitis.[18] Occasionally, patients with S.L.E. have been found to have chronic active hepatitis,[14] and patients dying of chronic active hepatitis and postnecrotic cirrhosis have had pathological evidence of S.L.E., but in general the liver is rarely involved in S.L.E. and there are usually no pathological findings in chronic active hepatitis suggestive of S.L.E. The finding of L.E. cells and antinuclear proteins in patients with chronic active hepatitis is of doubtful significance, although Bartholomew[5] believes that all patients with L. E. cells and hepatic disease are patients with either a lupus diathesis or overt S.L.E., who develop viral hepatitis.

TREATMENT[10 16 17 18 19 21]

The management of chronic active hepatitis includes specific therapy directed against the progressive hepatitis and the treatment of the stigma of chronic liver disease.

Mackay[17] did a comparative study on the effectiveness of various methods of treatment in chronic active hepatitis, and found that corticosteroids were superior to all other forms of therapy. Most other investigators[10 18 21] agree with Mackay and have found that the administration of steroids during the acute stage of the disease, is followed by reduction in fever and jaundice, improvement in skin rash, rheumatic complaints and other systemic manifestations, return of the menses, and reduction in the size of the liver and spleen. There is usually a prompt fall in the S.G.O.T. levels, the serum gamma globulin gradually falls, sometimes becoming normal after months of treatment, and the serum albumen tends to rise.

If steroids are given continuously as maintenance therapy, they are capable of suppressing clinical and laboratory evidence of activity.[10 17 18 21] However, it is debatable whether or not continuous steroid therapy successfully halts the progressive liver cell destruction and resultant fibrosis. Sherlock[21] and Read[19] examined serial liver biopsies of steroid treated patients and found that progression to postnecrotic cirrhosis continued irregardless of therapy. Mackay[16] and Maclachlin[18] are undecided as to whether continuous steroid therapy prevents continuing hepatic fibrosis, although Maclachlin[18] noted histological improvement in two of three patients in whom serial biopsy was done. Kern[10] found histological improvement with no progression of hepatic fibrosis in over 50% of his cases, but he also noted that steroid therapy was beneficial only in those patients whose original biopsy revealed inflammatory activity. There was no improvement in those patients whose liver biopsy revealed postnecrotic cirrhosis without active inflammation.

The usual method of steroid management in chronic active hepatitis is to determine the daily dosage arbitrarily, as enough to control or diminish the signs of hepatitis. This varies from 15 to 80 mg. of prednisone per day.[10 17 18 21] The initial close is gradually reduced

to the minimal amount which is capable of suppressing the disease. Maintenance dosage is most easily determined by balancing dosage against repeated S.G.O.T. levels, and is usually about 15 - 25 mg. of prednisone per day. The patients become dependent on steroids so that rapid reduction in dosage or diminution below a certain minimum (usually about 15 mg. per day) leads to exacerbation of symptoms. Rarely, a patient can be taken off steroid therapy without a relapse, but in most cases, carefully controlled, long term maintenance therapy is necessary to control the activity of the disease.

The most common complications of maintenance steroid therapy in these patients are acne, moon facies, and abdominal striae. Fatal infections, exacerbations of peptic ulcers, severe osteoporosis and thrombophlebitis with pulmonary embolism all occur.

Bed rest and hospital regime are beneficial in the management of chronic active hepatitis, and broad-spectrum antibiotics, such as tetracycline, have proved useful, as these patients are susceptible to secondary bacterial infections.[16 18] Mackay[17] found that 6-mercaptopurine (6-MP, 50 to 100 mg. per day) and azothioprine (100 to 200 mg. per day) were useful agents in the long term management of chronic active hepatitis.

The stigma of chronic liver disease such as portal hypertension, ascites, bleeding tendencies and hepatic coma should be treated along usual lines.

Prognosis[6 15 17 18 21]

The prognosis of chronic active hepatitis is poor, as the disease usually progresses relentlessly, with relapses and remissions, to liver failure. Bearn et al,[6] found that most patients succumb to their disease within ten years of onset. Most other investigators[15 17 19 21] noted that the average duration of the disease was three to five years, the patients dying of progressive liver failure which was often aggravated by ulcerative colitis, severe bleeding, bronchopneumonia and renal infections. Sherlock[21] found that steroid therapy, although it relieved clinical symptoms, did not increase the survival time of the disease.

Summary

Chronic active hepatitis is a clinical, laboratory and pathological entity which occurs most frequently in young women. The onset of the disease may be the insidious development of fatigue and jaundice, or it may begin acutely with all the hallmarks of acute viral hepatitis. Systemic manifestations, which resemble S.L.E., may be present, and may precede or accompany the liver disease. The course of chronic active hepatitis is one of relapses and remissions, leading eventually to death from liver failure.

The liver pathology shows evidence of liver cell necrosis, resultant fibrosis, and an inflammatory mononuclear cell infiltration, which at times may be quite massive. Towards the end of the disease, the liver presents the typical picture of post-necrotic cirrhosis. Only rarely is pathological evidence of a systemic disorder found. The laboratory findings include abnormal liver function studies, various serological abnormalities, and protein abnormalities with a striking increase in the gamma globulin fraction. The severity of these laboratory findings tends to parallel the severity of the liver disease.

The etiology and pathogenesis of chronic active hepatitis is obscure, although viral and autoimmune processes are most frequently invoked in an attempt to explain the causation and perpetuation of this disease.

Steroid therapy is the management of choice and if used continously, will suppress evidence of the disease, although it may not halt pathological evidence of disease or prolong the life of the patient. The prognosis is bleak, as the average duration of chronic active hepatitis is less than five years, with most patients being dead within ten years.

ACKNOWLEDGEMENT

Many thanks to Dr. E. J. Prokipchuk, Internist, St. Michael's Hospital.

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Ulcerative Colitis And The Ileostomy Patient

J. Richman 6T7

Ulcerative colitis is defined as an idiopathic non-specific inflammatory disease involving primarily the mucosa and submucosa of the colon.

There have been many theories as to the cause of this entity, the most popular being, an autoimmune disorder, a hypersensitivity or allergic reaction, bacillary dysentery, overactivity of the parasympathetic nervous system, and finally, psychogenic.

It is this last theory which is also ingrained in the hearts of so many physicians and which has caused more harm to the patient than good that I wish to discuss.

It is a well known fact that every person under stress of any sort will have hyperactivity and hypersecretions of the G.I. tract. In most cases, this results in little more than a bit of indigestion, or at most, severe diarrhea. But take a person with a badly diseased colon and add this same mild stress, this will only aggravate the disease and not give it a chance to heal.

It was thus noted for years that when a person had a severe attack of U.C., this was precipitated by severe stress or worry and the latter was thus falsely assumed to be the cause of the former. But when careful studies of these people were taken concerning their disposition before they had ulcerative colitis, it was found that they were not the neurotic personality that was once thought. In more cases than not, these people had assumed a responsible role in society; but once U.C. manifested itself, then these people were neurotic secondary to the disease process.

This was proven, for when these people came to operation and had their diseased colon removed, their whole life and personality took an immediate turn for the better. They became amiable again, more relaxed and within months were back at work, assuming a useful life and loving it.

So why do so many physicians think that this disease is in some way psychogenic? When the physician sees the patient with U.C. it is usually, if not always, many months or even years after these symptoms have appeared, and secondly U.C. is never cured except by surgery; and so these patients which remain under his care continue to exhibit a pseudo-necrotic behaviour, and thereby those who are turned over to the surgeon, remain under the latter's care who sees then return to normal. So the internist rarely gets to see the dramatic change in behaviour which takes place once the diseased or toxic colon is removed.

"The chief problem centers about the indications for surgical intervention. Considerable variations exist as to the threshold levels of resistance or capitulation on the part of the physician to permit the operative management of his patient. Perhaps the one point about which there is most confusion relates to the emotional disorders of the patient. The disease in the colon may be brought under control medically, but the patient's emotional disorders may continue to be incapacitating. Freed of his colon, many of his emotional ills may disappear, but is this an indication for colectomy? Most believe not." [1] Thus the emotional disorders remain even when the disease is under control.

In my experience of meeting over one hundred people with ileostomies my first year post-operatively, and of visiting and helping to take care of about five or six during the same time, both pre- and post-operatively,[1] was amazed to find such a variety of personalities; responsible business executives, engineers, plumbers, and hockey players doctors and housewives et cetera. I could not find any similarity between any of these personalities, nor did any of them appear neurotic, although their stories of how they were, before they had an ileostomy, did not indicate this.

Thus in observing over one hundred patients with ileostomies and some ten-to-twenty persons with U.C. in the last three and one-half years it was seen that in almost all of them that their emotional disorders were secondary to the disease. Having talked with several surgeons since, the same observations were made in their cases post-operatively. Dr. Kergan, chief of surgery of T.G.H., told me he has only seen one patient out of hundreds whose U.C. could be cured by psychiatric aid, and the rest were only cured by the removal of the diseased colon.

What then, we ask, causes the worry which precipitates an attack of U.C. when if all the patient has to do is relax and not worry, he will, it is hoped, get better?

This is foolish, for the disease will never disappear unless the cause is found and treated, and at this time the cause is unknown. Therefore you are asking these people to go through the rest of their lives not worrying. You are telling women to not worry about their children when they are out late at night or when they are sick. You are asking responsible business men not to worry about their work. You are asking people, sick for years with this chronic disease not to worry about the fact that their family is under severe financial strain while the breadwinner is in the hospital and cannot earn

any money, let alone not to worry about where he will ge the money for his medical bills. Also U.C. patients are practically non-insurable.

Then to top it all off, if you had to run to the washroom fifteen to twenty times a day, were severly anorexic and couldn't eat a thing, had a sour, bitter taste in your mouth, had cramps in your belly, were constantly passing smelly gas, and everytime you went to the washroom saw blood in your stools and then some doctor looked you straight in the eye and told you not to worry, then, you would feel as if you wanted to break down and cry. The best reassurance a patient with U.C. can have, is to know that if his disease gets worse, it can be cured by surgery and if it gets better on conservative treatment, then all the better (although remember the emotional disorders will remain in many patients).

Ileostomy surgery was, and in some cases still is, a dirty word amongst internal medicine men because:

1) Medical men hate to lose patients, which they feel can be treated conservatively, to the surgeon.

2) They feel that people with U.C., since they are emotionally immature, cannot cope with the thought of wearing a bag on their side for the rest of their lives.

3) That persons with ileostomies are of no good to society and can only stay at home and take care of themselves, and thus become more neurotic.

Well, the first is bad medicine, for when medical treatment fails then the patient must be turned over to the surgeon. I have seen too many people lose months and years out of their lives and even become operative risks as the doctor almost waited too long, hoping to pull it out of the fire.

The second and third reasons are totally erroneous for life with an ileostomy is in no way a handicap, and at most, a slight inconvenience. In cases where it is difficult to make a decision, the patient himself should be allowed to choose whether or not he is capable of living with an ileostomy once all the facts are laid before him. The physician has no right to make the choice for him.

Too many times the patient is kept from knowing of the surgical possibility since it is felt he cannot cope with it but if they are not getting better and they see the physician can do nothing to help them, then they think they are going to die. This is a fact and no one should be left to think this, when there is no truth in it, simply because the physician forgets himself and plays God.

So let us discuss what an ileostomy has to offer. There are no limitations placed on a person with an ileostomy that I know of. We are warned to keep away from contact sports, such as football and hockey, only because the bowel protruding from the anterior abdominal wall is vulnerable but one ileostomist I know still plays hockey and many play touch football with some blocking on the line. Why? Because we forget we have ileostomies and live normal lives. Stupid? Perhaps, but nothing has happened yet.

The patient with U.C. has three choices:

1) The possibility of getting worse, wishing to have nothing done and dying, in the severe acute fulminating type, or in the chronically severe type.

2) The possibility of, (a) living a relatively normal life with mild U.C., (b) living a chronically ill life with U.C.

3) Having an ileostomy.

Let us look at 2 (b) for it is here where there is difficulty in arriving at a decision of surgery. With U.C. the limitations and complications are many including loss of weight, dehydration, anorexia, pain, inability to work with loss of income, continuance of hospitalization and medication, ill-tolerated diets, no alcohol, limitation of exercise and sports, the strain on the rest of the family, and last but not least, the possibility of cancer. But with an ileostomy there are none of the above limitations and one can live his life any way he wishes.

The severe chronic U.C. patient is a chronic invalid and nothing more. He can't enjoy an argumentative intellectual discussion for it will upset him. He can't yell at his kids; he can't strain himself in any way; he must constantly be on medications, hundreds of pills a month and never show any results, while the ileostomist literally hasn't a care in the world in comparison.

The appliances made today are marvellous; they stay on in some cases over a week and even then it only takes one hour to change and cleanse an appliance. The bag is emptied thru a spout at the bottom about three times a day, a process which takes only two to three minutes each time. t is well worth it when one thinks of the many, many hours spent every week in the washroom with U.C.

The good appliances are odour-proofed and are designed to fit the body contour so women can wear the tightest fitting clothes and even two-piece bathing suits and one can never tell they are wearing an ileostomy appliance. The appliances also fit so well that swimming, waterskiing, skiing, basketball and any other sport one can think of can be played in comfort and without any worry.

Ileostomy surgery and appliances have made life so wonderful for people with severe chronic U.C. that when medical procedures fail to benefit a person with U.C., surgery should seriously be considered.

*Indications for Operation

1) Acute fulminating disease with uncontrollable hemorrhage, toxic megacolon, or a continued downhill course despite aggressive medical management.

2) Complications of acute or chronic disease, such as stricture with partial or complete obstruction, perforation of the colon, peritonitis, abscess formation, fistula formation.

3) Medical failure; that is, chronic invalidism or the continued presence or progression of chronic bleeding, arthritis, dermatitis.

4) Carcinoma, proved or suspected. The onset of carcinoma in U.C. patients is at an average age of forty-two years after an average duration of disease of fourteen years.

Some Aspects of Preoperative Care

The patient should be told he is going to have an ileostomy and a person with an ileostomy from the Ileostomy Association should be called in to visit.

The person with the ileostomy will never discuss with the patient the technicalities of the operation nor any medical complications but only of how the patient can once more return to a normal life. The patient, seeing someone healthy, strong, and active, and knowing he can return to a useful life, will be better off psychologically to face surgery.

Some Aspects of Post-operative Care

The patient should be taken care of from the first with the aid of a person from the Ileostomy Association. Ileostomists have suffered through this hospitalization before. They put on and take off their own appliances all the time. Many have taken care of patients in hospital and have more experience than the surgeon and the nurses, when trouble arises concerning the stoma, the skin about it and other matters too minor to concern the medical staff, but very frightening to a person who is about to start life with something entirely new and different. The Ileostomy Association will never interfere or advise the medical staff in a hospital if, it is felt in the slightest, this advice is not wanted.

I have seen patients with their skin burned right off from the high enzyme containing fluids pouring out of the ileostomy simply because a nurse could not put on an appliance properly, and refused to let others do so since it was her patient. It have seen doctors send home patients in the same state, never knowing how to take care of their ileostomy or where to go for an appliance.

*NOTE—Many people are living today with mild forms of U.C. and are carrying on good useful lives and are only mildly inconvenienced and it would be foolish to consider major surgery in these cases.

PLACEMENT OF THE ILEOSTOMY
IN THE LOWER RIGHT QUADRANT

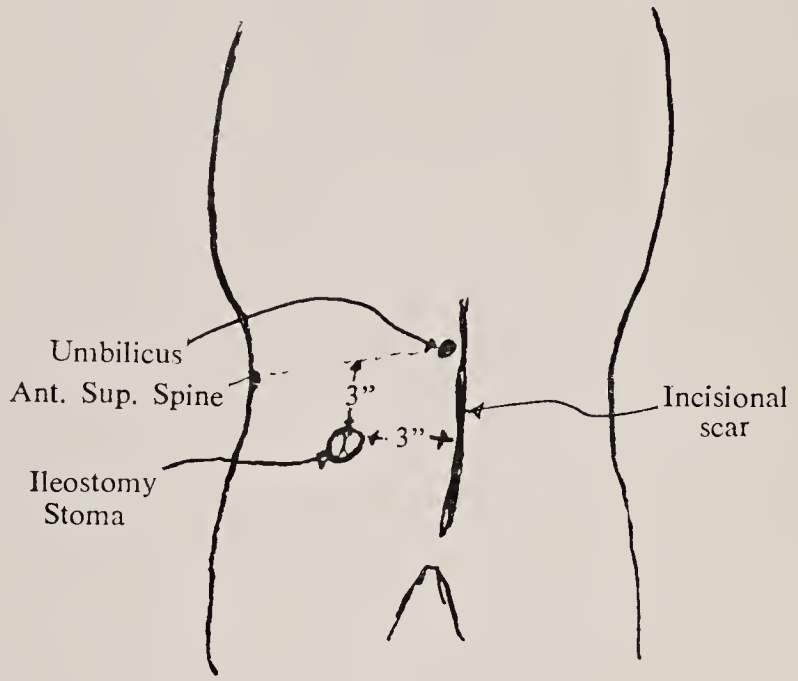

FIG. 1

They are literally cripples until they can find someone to help them.

Thus the Ileostomy Association plays a vital role in their quick recovery and with their assistance, a permanent appliance may be worn, at the latest, ten days postoperatively. By attending meetings of the Association, an ileostomist can learn, through other people's experiences, why certain things are happening. With a hundred phone numbers, at their side, of people who have all gone through the same experiences, they soon lose their apprehension and quickly learn how to take care of themselves without having to bother their physician about every little thing. The Ileostomy Association of Toronto can be reached by calling the Academy of Medicine in Toronto.

Finally I would like to talk about a few of the practical points of the surgery itself, for no matter how technically sound the operation is, the patient must carry this around with him for the rest of his life and it might as well be done in such a manner that he will have a minimum of difficulty in taking care of it.

The ileostomy is best placed in the right lower quadrant, midway between the umbilicus and the anterior superior spine and two to three inches below an imaginary line drawn between these points. The incision is best placed just to the left of the umbilicus, at least 3" from the centre of the ileostomy. (Fig. 1)

1. This allows the ileostomy to be low enough that one can wear bathing suits and summer shorts without an appliance showing over them.

2. This places the ileostomy in a position where the contour of the body is such that an appliance cannot be seen through tight clothing.

3. The incisional scar will be far enough from the ileostomy that the appliance will fit over even smooth skin only and its edge will not be raised by scar tissue,

causing the appliance to lift sooner than it otherwise would.

The diameter of the stoma should be no more than one inch as this is more than sufficient to allow the feces to escape and a larger stoma would be ugly to look at and necessitate a very large appliance which may be uncomfortable and more easily seen through clothing.

The length of the stoma should be from ½ - 1" long and thus no longer than 1 - 1¼" at the end of the operation for if the ileostomy is anchored properly it will not detumesce, to less than half its size. If the stoma is less than ½" long, then the chance that fecal matter will undermine the appliance is greater. If the stoma is longer than one inch it looks ugly and instead of standing straight out from the abdominal wall, it flops down and raises minor difficulties when changing the appliance. Also this leaves more bowel exposed to trauma. As the appliance itself is only ½" off the surface of the skin, then thebowel need be only this long to drop the fecal contents into the bag.

The technical aspects of the surgery is dealt with very well in the text SURGERY by Moyer, Rhodes, Allen, and Harkins, except for two points. They state that the stoma should be placed at or near waistline as a belt is worn for support. The belt will not pull the appliance out of position, as they suggest, when the appliance is placed lower in a more suitable position functionally and cosmeticaly. In fact the appliance is better anchored by a belt in this lower position as with everyday movements and bending, the appliance tends to shift downwards in the lower position and is held in equilibrium by the belt pulling up. We know this from experience and if the appliance is at waistline, especially as most ileostomists have 'spare tires', it will tend to shift up on bending and with the belt pulling in the same direction, it is not stable. But if it is below waistline it tends to shift down and the belt pulls it up and it is in equilibrium and stable.

The second point they make is that the bowel should only be anchored by its mesentery to the abdominal wall internally and that "No sutures should be placed in the bowel segment as it transverses the abdominal wall lest a fistula develops. . . . This internal anchoring of the mesentery to the parietes is said to eliminate the possibility of three postoperative complications of ileostomy: internal hernia, rotational volvulus of the internal ileum, and prolapse of the ileum through the ileostomy".[1] It has been shown that the latter procedure will not prevent these complications from arising. But, only if sutures are placed through the bowel segment itself with special care not to go through the mucosa, anchoring it to the anterior abdominal wall superiorly along the ligamentum teres hepatis to where it joins the falciform ligament, as well as to the abdominal muscles where it leaves the abdomen, before it is inverted, can

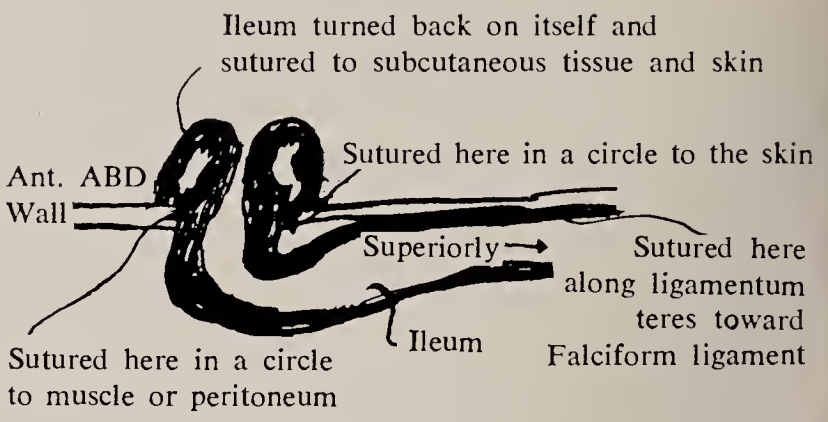

FIG. 2

one be almost 100% sure these complications will not arise. At King's County Hospital, New York they are being done this way (as was mine here in Toronto but it is not common practise here) and there have been no reports of fistulous tracts forming, as long as the surgeon did not penetrate the mucosa. (Fig. 2) Also at least 8, preferably 16, interrupted diagonal sutures should bind the mucosa to the skin or it will pull away readily predisposing to infection, poor healing, and excess scar formation.

In conclusion I would like to say that one should never condemn a man until he is proven guilty even though he may be found holding the gun. He may have picked it up by mistake. Thus one should never accuse a man of getting ulcerative colitis because he is a worrier. Instead, it could be that a man with U.C. has something to worry about. Also the medical profession does not always have the time or the knowledge to deal with every phase of a person's care especially when it comes to ileostomies. There is an organization here, ready and willing to help. Finally, an ileostomy is the easiest thing in the world to live with and if I had to lose a part of my body, and I could make the choice and know what I know now, without any hesitation, I would choose my colon.

SUMMARY

1. Ulcerative colitis is not, as many physicians use to feel, psychogenic, but causes the nervous disorders seen with it.

2. The ileostomy is the ony cure of U.C. with over 98% five year survival, the other 2% being in the old age group, cancer group, or were operative risks at the time of operation. The ileostomist may carry on a completely normal life with few, if any, limitations. This does not affect sexual intercourse nor does it keep a woman from having children.

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*Structural Aspects Of The Immunoglobulins**

M. A. Baker 6T6

Introduction

Much work was done to characterize the anti-infective properties of antibodies by such men as Jenner, Pasteur, and von Bering in the latter half of the nineteenth century.

It was Landsteiner, however, who pioneered the chemical approach to immunology with his study of blood groups and isohemagglutinins for which he received the Nobel Prize in 1930.[1,2] In recent years the horzions of immunology have widened to the extent that no area of medical science remains uninfluenced. Nevertheless, the biochemistry of the immune globulins remains as one of the most vital aspects of the immunological field.

Since the time of von Bering's postulate, the functioning unit of immunology has been the antibody. Currently, however, considerable interest is being focused on dissecting the molecular unit into its component parts, and attempts are being made to determine what role the subunits are playing in the functions of the whole antibody.

Terminology

Twenty-nine years ago, Arne Tiselius defined the gamma globulins as that fraction of the serum proteins which migrated most slowly on electrophoresis. Among the serum proteins the unique characteristic of the gamma globulins is their antibody activity; they have also been shown to possess a degree of chemical heterogeneity which has not been observed in other serum proteins. Increasing knowledge of this diversity has lead to difficulty in defining what is actually meant by "gamma globulin". A definition based solely on electrophoretic mobility is now clearly inadequate.

It has been suggested by Fahey[3] that the term "gamma globulins" should include all the serum proteins known to be formed in plasma cells and lymphoid cells. Heremans[4] proposed the use of the term "immunoglobulins" to include all the proteins produced in plasma cells. The latter term has now been widely accepted since it avoids ambiguity with the electrophoretic terminology and stresses the biological function of these proteins. Immunoglobulins are more exactly defined as "proteins of animal origin endowed with known antibody activity, and certain proteins related to them by chemical structure and hence antigenic specificity."[5] The related proteins include myeloma proteins, Bence-Jones proteins and other naturally occuring subunits of the immunoglobulins. Much confusion arose from the fact that several independent groups of investigators have studied the immunoglobulins and have applied different names to components that now appear identical. An international nomenclature has recently been introduced which eliminates this ambiguity.[5] The four major classes of immunoglobulin molecules found in normal serum are designated as follows:

Table 1.
International Terminology of the Immunoglobulins.

Name	*Synonyms*
IgG (or γG)	γ, 7sγ, 6.6sγ, γ2, γss
IgM (or γM)	γ_1M, β_2M, 19sγ, γ-macroglobulin
IgA (or γA)	β_2A, γ_1A
IgD (or γD)	

The two major kinds of polypeptide chains present in the immunoglobulins are called respectively, "heavy chains" (or "H-chains") and "light chains" (or L-chains").

Structure

Certain of the physico-chemical properties that distinguish IgG, IgA, and IgM have been described in detail, the most important of which are the molecular weight, sedimentation coefficient, and electrophoretic mobility.[3] (Table 2, Fig. 1.) The heterogeneity exhibited by the immunoglobulins is far greater than that seen in any other of the serum proteins and has been observed in the immunoglobulins of all species studied.

Studies of the primary and secondary structure have uncovered only limited information about the immunoglobulins.[3,4,6,7,8] Optical rotatory dispersion studies show that these proteins are not alpha helixes, a finding that correlates with the very high proline content discovered on amino acid analysis. It is suggested that the most likely secondary structure is a "pleated-sheet" arrangement ("extended beta-conformation"). The relationship of amino acid composition to antibody specificity is being elucidated by the chromatographic "finger printing" technique; however, neither the complete primary structure nor the tertiary structure has been worked out for any of the immunoglobulins.

*Abstracts from "STRUCTURE AND FUNCTION OF GAMMA GLOBULIN". Awarded the Charles E. Frosst Scholarship in 1965.

Table 2.
Physicochemical properties of the Immunoglobulins.[3]

Property	IgG	IgA	IgM
Molecular Weight	150,000	160,000 or more	1,000,000
Sedimentation Co-efficient (Svedberg units)	7S, 6.6S or 6.5S	6.6S to 15S	19S, 18S or 24S
Electrophoretic Mobility (predominant region)	mid-γ	slow-*B*	fast-γ

Fig. 1.
Electrophoretic Distribution of the Immunoglobulins.[3]

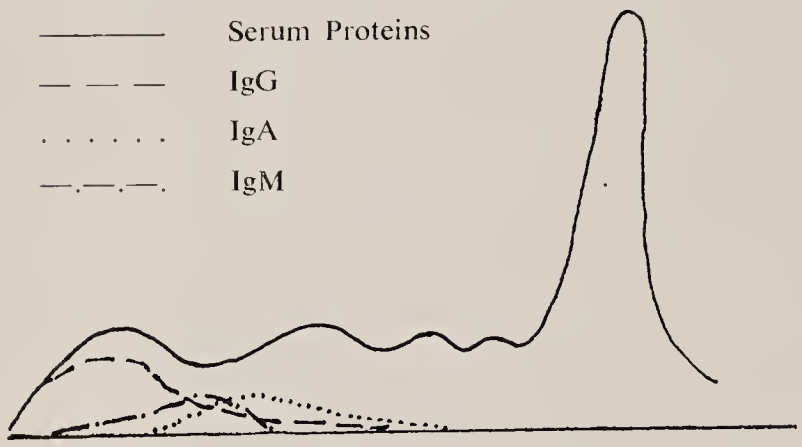
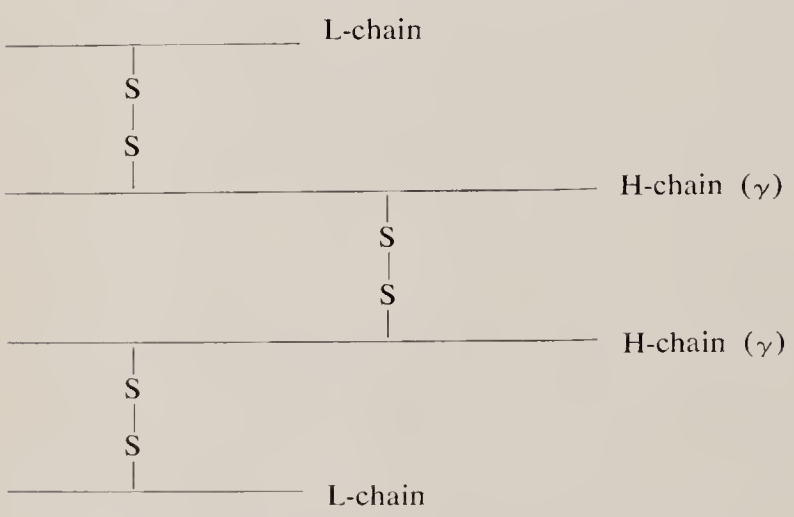


Fig. 2. Diagrammatic Structure of Immunoglobulin G.[4]



The technique of splitting the protein molecules by means of enzymes or reducing solutions has yielded some understanding of the polypeptide chain structure of IgG.[3 4 5 6] As a result, several models have been proposed, the most popular of which is shown in Fig. 2. Here IgG is pictured as having four polypeptide chains: two heavy chains and two light chains, which are arranged symmetrically and held together by disulphide bonds.

All the human immunoglobulins cross-react with antisera prepared against any one; however, each type of immunoglobulin (except the micro-globulins) also has a class specific determinant.[6 9] This observation suggests that some parts of the molecular structure are common to all four types of immunoglobulins and that other parts are distinctive. Starch gel electrophoresis has shown that all the light chains have the same mobility and that the heavy chains of each immunoglobulin type have different mobilities. Amino acid analyses and studies of allotypic antigens have supported the hypothesis that the human immunoglobulins carry a common light chain and a distinctive heavy chain. The heavy chains are designated by the Greek letter which corresponds to the Roman letter of each immunoglobulin, as follows:

Heavy Chain	*Molecule*
IgG	γ-chain
IgA	α-chain
IgM	μ-chain
IgD	δ-chain

The light chains are comprised of two antigenically distinct species called κ(kappa) chains and λ(lambda) chains. These occur with apparent random distribution amongst the immunoglobulin molecules. The two light chains of a single molecule are always of the same species, so that an IgG molecule always contains two heavy γ-chains but may have two light κ chains or two light λ chains. Molecular formulas may be written to represent the structure of any immunoglobulin molecule, *e.g.* IgG may be symbolized as $\gamma_2\lambda_2$ or $\gamma_2\kappa_2$ and IgA as $\alpha_2\lambda_2$ or $\alpha_2\kappa_2$ and so on. IgM is written as $(\mu_2\lambda_2)_n$ or $(\mu_2\kappa_2)_n$ due to its high molecular weight.

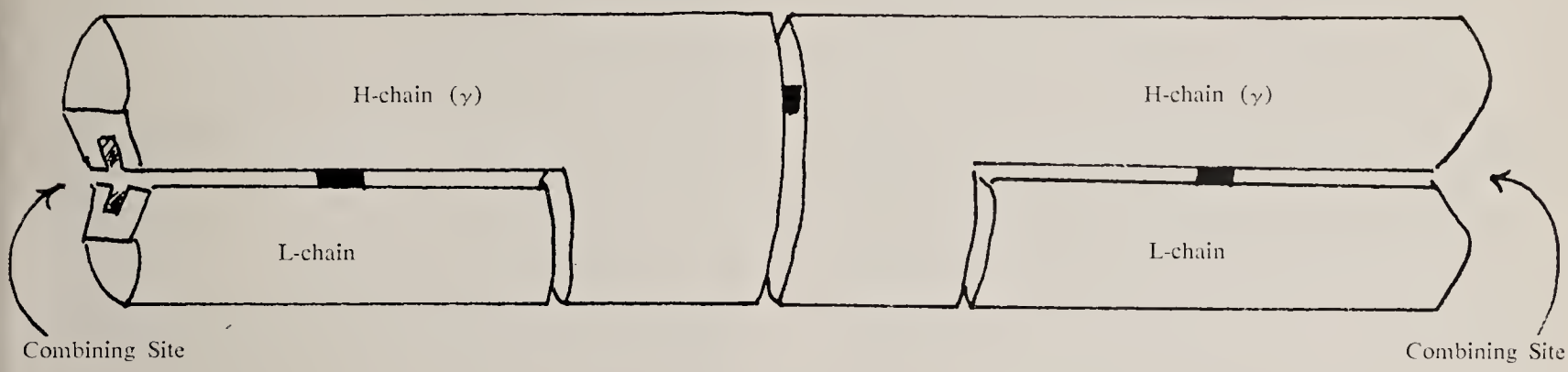
The three dimensional structure of IgG and IgM have been calculated by hydrodynamic data[6] and more recently by electron microscopic studies and low angle x-ray scattering experiments.[7] The results of the three methods correlate well and suggest that the IgG molecule is a cylinder of elliptical cross section (Fig. 3), and that IgM is roughly spherical.[7] The cylindrical IgG molecule resembles the two dimensional model in being composed of two symmetrical halves, each composed of one γ-chain joined to an L-chain by a disulphide bond. The γ-chains of the two halves are in apposition and are linked by a single disulphide bond. It is assumed that each polypeptide chain is folded to fit into the overall cylindrical shape.

There is some controversy as to the location and composition of the antibody combining sites.[4 6 11 12 13] In the cylindrical model there are two antibody combining sites, one at each end of the cylinder, represented as shallow crevices between the L-chain and the γ-chain. This location of the sites accounts for antibody bivalency and is consistent with electron micrographs showing rod like antibody molecules with virus particles at both ends.

Function as Related to Structure

The four immunoglobulin classes have been shown to have distinctive structural features. One might expect, therefore, to see a division of antibody function which corresponds to the different structural classes. Several of the human antibodies have been classified

Fig. 3. Three Dimensional Model of Immunoglobulin G.[7]



into structural groups, however a certain amount of duplication occurs. A single antigen may stimulate the formation of both G and M immunoglobulins, but it is not certain that both antibody forms are directed at the same antigenic site.[3] No distinctive function has as yet been assigned to IgD.

Antigenic stimulus by viruses, bacteria, and animal cells as well as proteins, carbohydrates and a variety of chemical haptens, give rise to immunoglobulin G.[3] Antibodies to red blood cells, however, are found largely in the IgM fraction. The molecular form of an iso-hemagglutinin may vary according to the blood group, so that an AO subject might have a different anti-B agglutinin that an AA or an OO subject.

The molecular form of the anti-erythrocyte antibody may be an important factor in determining the production of hemolytic disease of the newborn, since antibody transfer across the fetal membranes is a highly selective process.[3] Experiments show that IgG is freely transferred whereas IgM and IgA are not, due in part to the chemical structure of the heavy chains.[14] The presence of a high proportion of IgG agglutinins in the maternal circulation would increase the likelihood of hemolytic disease in susceptible infants.

Human reaginic antibodies are usually found exclusively in the IgA fraction, therefore, specific removal of IgA from the sera of atopic individuals will eliminate all detectable skin sensitizing activity.[15] Furthermore, reaginic antibodies do not cross the placental barrier, probably due to lack of the γ-chain structure which permits selective transfer of IgG across the fetal membranes.[14]

Complement fixation is known to occur with antibodies belonging to both IgG and IgM fractions, but the IgA antibodies of the same specificity seem to lack this capacity.[17,4] Anaphylaxis seems to occur in the presence of IgG antibodies but not IgM antibodies. IgA antibodies to milk have been discovered in infants afflicted by "crib death", a condition in which previously healthy infants are found dead for no apparent cause. It is suggested that aspirated milk causes an antibody response in the lungs leading to sudden death.[16]

Conclusion

The details of antibody substructure are only beginning to be uncovered, but the degree of complexity of that substructure is already appreciated. Only by resolution of this complexity will it be possible to understand the basic mechanisms of the immune response.

ACKNOWLEDGEMENT

I would like to thank Dr. J. H. Crookston of the Department of Medicine, University of Toronto, for advice and encouragement in the writing of the original essay.

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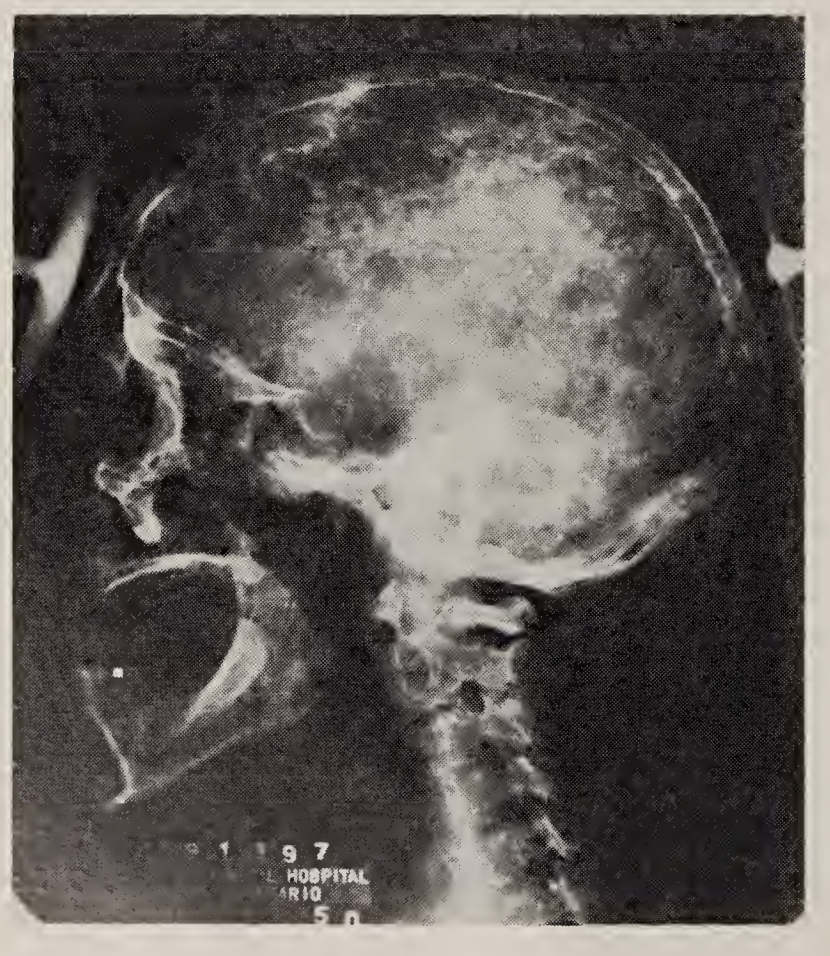
On Inspection - Questions

N. D. Colapinto 6T7

1. This is an easy one.
   a. What features are present?
   b. What is your diagnosis?
   c. List the features which differentiate this condition from rheumatoid arthritis.

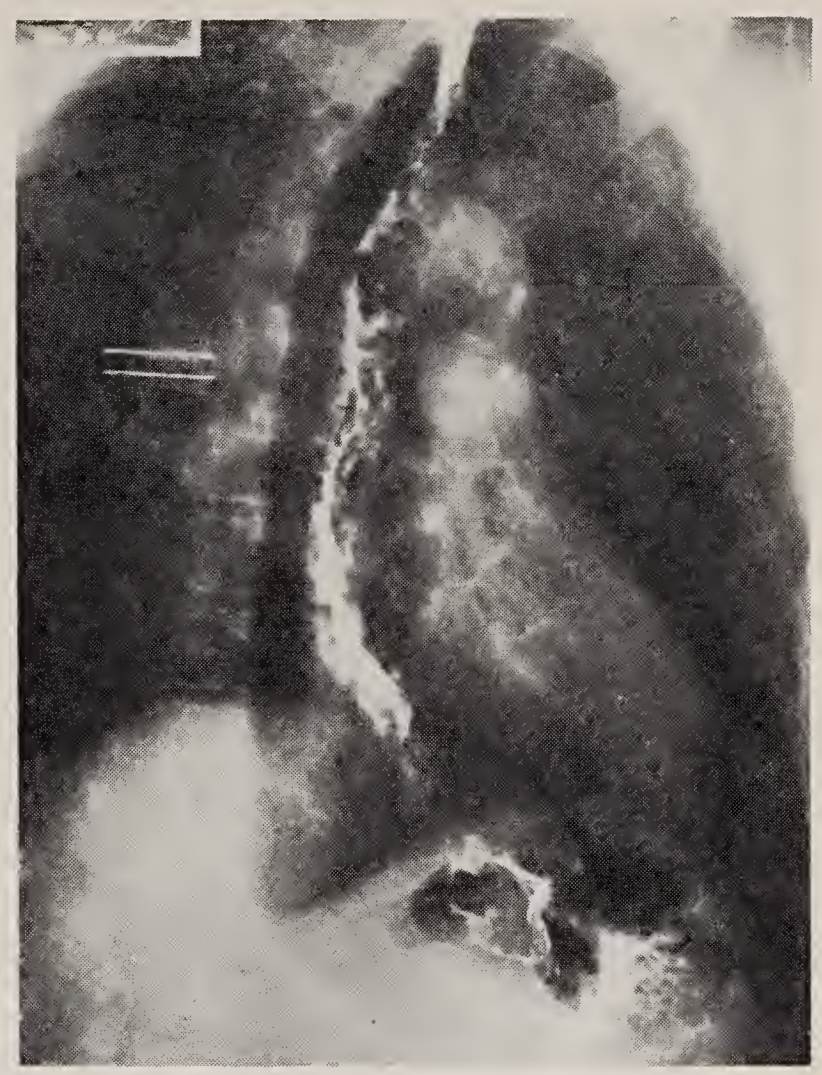


2. Patient was a 48 year old male with a history of headache, weakness and a 25 pound weight loss. Total serum:
   protein—12.5, albumin—2.8, globulin—9.2.
   a. Diagnosis?
   b. Clinical picture?

3. 75 year old male patient.
   Acid phosphatase 7.4, Alkaline phosphatase 77.
   a. Provisional diagnosis?
   b. What further procedures would you carry out to establish the diagnosis?
   c. List the conditions causing urinary obstruction.

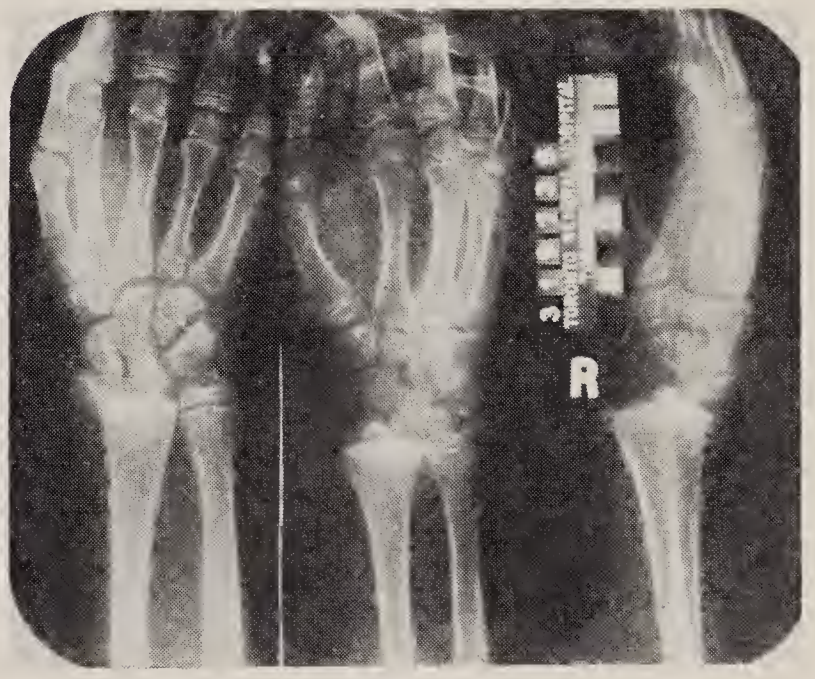
4. a. What is the primary disease shown in this film?
   b. What lesion has been superimposed on this primary disease?
   c. Classify the main causes of intestinal obstruction.

5. a. List the abnormal findings in this film.
   b. What is your diagnosis?
   c. How many complications, sequelae, and associated lesions can you name?



7. 53 year old male developed tarry stools and weakness.
   a. What are the lesions shown on the x-ray?
   b. Classify the clinical forms of cirrhosis of the liver.

6. a. What procedure is being carried out here?
   b. How many vessels can you name?



8. 15 year old male patient fell on his outstretched hand.
   a. What features are visible in the film?
   b. What is the name given to the deformity produced?
   c. Diagnosis?
   d. Treatment?

(Answers on page 209)

*Electron Microscopic Autoradiography Of Hematopoietic Cells Using Iron 55**

S. Lofsky 6T6
A. F. Howatson, Ph.D.†

Autoradiography is a scientific tool using radioactive isotopes to determine the localization of a substance in tissues or cells. A radioactive form of the substance in question is fed either *in vivo* or *in vitro* to the tissue and the radioactive substance is taken up by the cells in the same way as the non-radioactive substance. For example, a hydrogen atom in thymidine can be replaced by a tritium atom, resulting in a widely used tracer substance, tritiated thymidine. After the cells have taken up the radioactive substance, the tissue is fixed and histological sections are then prepared and mounted on slides. These slides are then dipped into a solution of photographic emulsion which consists of radiation-sensitive silver bromide crystals in gelatin. The slides are then dried and stored in the dark. The isotopes in the tissue sections emit ionizing radiations which expose those crystals of the photographic emulsion lying over that particular part of the cell. After a length of time which depends on the nature and amount of isotope used, the slide is developed and fixed like an ordinary photographic plate. This results in the formation of black dots or "label" overlying those areas of the tissues which contain the radioactive substances. In this way the fate and localization of substances fed to cells can be followed. With light microscopy auto-radiography (LM-ARG) it is possible to localize uptake to cells and to major cell components (nucleus, cytoplasm). In order to localize uptake to cell organelles electron microscopic autoradiography (EM-ARG) has been introduced.

Electron microscopic autoradiography has been in use for only the last 5 years. The process is essentially similar to LM-ARG. The specimens are embedded in special resins and are cut into exceedingly thin sections. Instead of being placed on a slide the sections are supported on minute circular copper meshes (grids). A film of emulsion is formed by dipping a wire loop[1 4] into diluted emulsion, removing the loop from the emulsion and allowing the thin film to gel. The grid is then coated by lowering the film of emulsion over it. This results in the very thin section being coated by a very thin layer of emulsion. After the grid has been stored for some time, it is developed, and then stained with electron dense materials to enhance contrast of cell structure. It is then observed in the electron microscope. One sees (Fig. 2) black wiggly-shaped grains overlying those parts of the cell which have taken up the radioactive tracer. For the most accurate localization, emulsions with very small silver bromide crystals must be used; and the beta particles or γ-radiation emitted from the isotope must be of sufficiently low energy that they will not be able to penetrate to areas of emulsion distant from the source of radiation.

Last summer we applied the methods of electron microscopic autoradiography to the study of iron uptake in hematopoietic cells. In light microscopy, the isotope iron 59 has been used in studies of this type. Unfortunately, it is less useful in EM-ARG because the high energy of the emitted radiation would result in poor localisation of the grains. Another isotope of iron Fe^{55} was then considered, and because of the very low energy of the radiations emitted, it has turned out to be ideally suited for EM-ARG. Although the use of iron 55 has been reported in the literature[2 3] in connection with LM-ARG, we could find no reports of its use in EM-ARG. We feel that its use in EM-ARG should be made known because of its possible use in future research.

In order that the iron would be taken up by cells, it was bound to the plasma protein transferrin. For this binding to occur, the iron 55 had to be in solution that was acidic but not so acidic as to denature plasma proteins. We found that iron 55 in N/10 HC1 would bind entirely to transferrin in serum. The manufacturer ordinarily supplies it in a solution of N/2 HC1, but will evaporate it down and dilute in N/10 HC1 if requested. Distilled water should not be used in diluting the iron as this will result in almost negligible binding to transferrin. The iron used was in the form of carrier free $Fe^{55}C1_3$, and the concentration used was 2 millcuries/ml (Nuclear Science and Engineering Corporation, Pittsburgh, Pa.). *In vivo* labelling* was accomplished by injecting ¼ cc. of iron 55 into a tail vein of a young mouse. After four hours the animal was sacrificed and the marrow was harvested by flushing both femurs with cold phophate-buffered saline. The resulting suspension of cells was then centrifuged, the supernatant decanted and the cell pellet fixed with glutaraldehyde.

For *in vitro* labelling ⅛ cc. of iron 55 was added to 1 cc. of mouse serum and left for half an hour to allow the iron to bind to the serum transferrin. Six cc.

*This work was done during the tenure of a summer studentship (by S.L.) at the Ontario Cancer Institute.

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*The labelling of cells *in vivo* and *in vitro* was carried out according to procedures developed by Dr. John Fowler at the Ontario Cancer Institute.[5]

of a cell suspension, obtained by flushing the marrow of young mice with a tissue culture medium (1066) was then added and the cells incubated at 35 degrees centigrade for two or three hours. The cell suspension was then centrifuged, the supernatant decanted and the cell pellet fixed with glutaraldehyde.

The specimens were then further fixed in osmic acid, dehydrated in acetone and embedded in Epon. Thin sections were cut and picked up on copper grids. The grids were then coated with Ilford L-4 nuclear track emulsion using the wire loop method, and after a period of storage they were developed in Microdol developer, washed in 1% acetic acid and fixed in Kodafix. The grids were then stained with uranyl acetate and lead citrate. After further washing the grids were observed in the electron microscope.

Results

Figure 1 and 2 are representative of the results obtainable using this technique. Figure 1 shows a low power view of cells in a marrow pellet. Almost every cell has some grains over it, but certain cells have a much greater number of grains overlying them than others. These cells are members of the erythropoietic series, and the grains probably indicate the presence of hemoglobin. Non-erythrocytic cells take up iron in smaller quantities, probably for the production of iron-containing enzymes such as cytochrome oxidase and peroxidase. Almost all the grains are directly over cells, illustrating the low background and the high degree of localization.

Figure 2 is a higher power view of a heavily labelled cell. This illustrates well the advantages of EM-ARG since cell organelles such as mitochondria are easily visualized. The grains are distributed mainly over the cytoplasm, but there are a few over the nucleus. Our preliminary observations suggest that these nuclear grains tend to be over the less dense areas of nuclear chromatin which are thought to be the sites of metabolic activity.

Discussion

The study of the uptake of iron by EM-ARG of hematopoietic cells using iron 55 is technically feasible and appears to offer distinct advantages over light microscopy methods. The morphological features of the cells are far clearer than in LM-ARG, facilitating the determination of cell types and the stage of differentiation of cells. Quantitative studies which correlate the stage of differentiation with the number of grains could be performed thus aiding the study of the kinetics of iron incorporation. Because of the precise localization possible with this technique, the route of iron as it is incorporated into the cell and into hemoglobin could be studied by providing timed pulses of iron 55 to these cells. Many other studies involving iron uptake are also possible. As an example, preliminary work has demonstrated that tumour cells in mice transformed by Friend virus take up iron, showing that the transformed

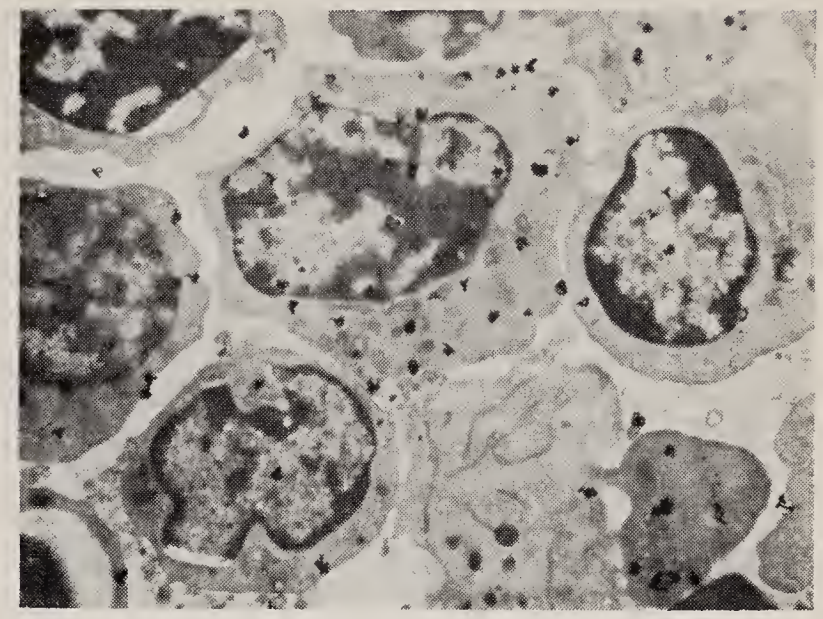

Fig. 1. Autoradiograph of a thin section of a pellet of marrow cells. The central cell is heavily labelled. The cell immediately to its right is lightly labelled.
Magnification: 15,000 X

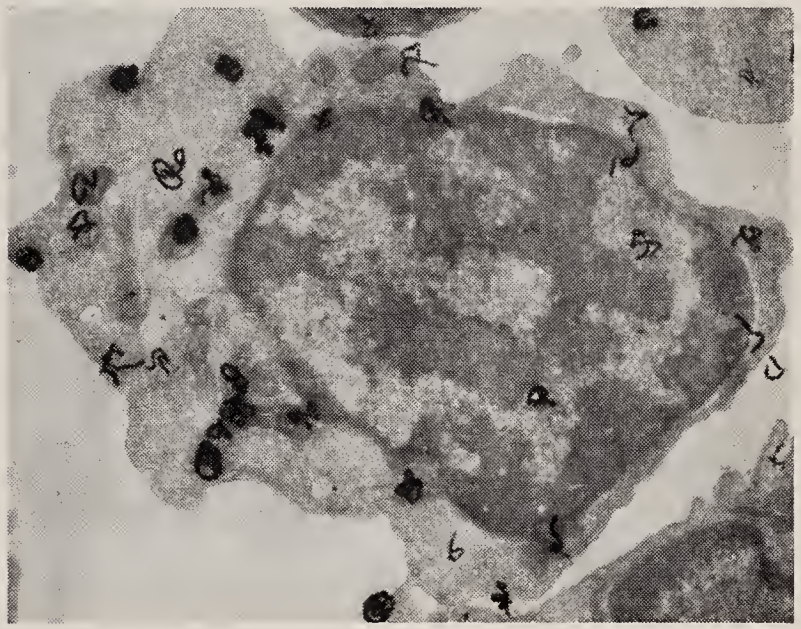

Fig. 2. Higher power view of a heavily labelled cell. Most of the label is over the cytoplasm but some overlies the nucleus, especially the less dense areas.
Magnification: 25,000 X

cell may have been originally a member of the red cell line. The advantage of electron microscopy in this study is that the transformed cell can be recognized by its morphology and the fact that typical budding of viruses from its surface can be directly visualized.

Summary

A technique for the use of the isotope iron 55 in electron microscopic autoradiography of hematopoietic cells is presented and the possible uses of such a technique are discussed.

ACKNOWLEDGEMENTS

Many thanks are due to Dr. John Fowler for his advice and assistance in labelling techniques and to Mrs. May Betlem for her excellent technical assistance.

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Cardiac Valve Transplantation: The Past, The Present And The Future

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INTRODUCTION

The recent rapid advance in cardiac surgery was stimulated to a great extent by the introduction of hypothermia,[1] and the development of the cardiopulmonary bypass. These allowed more intricate procedures to be carried out by increasing the length of time the heart could be arrested without subsequent anoxia. With the aid of these techniques, great strides have been made in valvular surgery with decreases in mortality for almost all procedures. This dramatic resurgence has sparked all manner of research on surgical methods of valve replacement, and has made cardiac surgery probably the most exciting specialty of our era. The purpose of this article is to acquaint the reader with existing and historical methods of valve replacement, and to put forth the hypothesis that the future of cardiac valve surgery lies in tissue grafting: homograft, autograft, and heterograft.

HISTORY

Because of difficulties with existing procedures for dealing with diseases of the aortic and mitral valves, the surgeons' thinking turned towards replacement of the valve with prosthetic devices. The development of the protheses for each valve will be described.

(a) *Aortic Valve*

Early procedures to relieve aortic stenosis (e.g. transventricular dilatation, aortic valvular comisurotomy, and debridement) and to correct insufficiency (e.g. bicuspidization) were, for one reason or another, unsatisfactory. Common complications were: 1) Production of insufficiency, 2) Tendency to restenose, 3) Difficulty in selecting proper patients since some procedures would only benefit certain types of lesion, and 4) High operative mortalities and-or poor long term results.

The first prosthetic replacements were cusp extensions. These were used in cases of insufficiency. Prosthetic leaves were sutured onto the existing cusp or cusps; no cusp material was removed. Materials used for the leaves were: 1) Dacron and silastic, 2) Teflon, 3) Teflon coated with polyurethane. This method has become obsolete due primarily to two complications: 1) Inability to produce complete competence of the valve in most cases, 2) Tendency for the prosthetic leaflets to stiffen curl and wear out with time.

The greatest step forward came with the development of the aortic ball-valve prosthesis by Starr and Edwards.[2] This consists of a silastic ball in a metal cage and is inserted in the aorta in a subcoronary position. It has proven the most satisfactory prosthesis so far and is in frequent use in aortic valve replacement in both stenosis and insufficiency cases. The complication most to be feared is thrombosis of the ball or cage with subsequent embolization. This necessitates maintaining the patient on a strict and perhaps lifetime therapeutic regimen of anticoagulants. This therapy, of course, must be carefully regulated for there is now the danger of vascular accidents due to the iatrogenic bleeding tendency. In spite of these complications there are many reports of low operative mortality (e.g. Effler[3] reports zero mortality in 27 patients).

Magovern has reported the development of the sutureless ball-valve prosthesis.[5] This device ressembles the Starr valve but has an opening in the top of the cage. It is inserted using retractable pins, thus the cloth and sutures of the Starr valve are eliminated. They had hoped that this would remove the main sources of thrombus formation, but this remained a problem since three embolic phenomena did occur in his series.[5] His overall operative mortality rate was 5.7% in 52 patients which is perhaps slightly higher than with the Starr valve. It has some advantages: 1) It is easier to insert, therefore the patient is on the pump a shorter time, and 2) the open cage reduces the problem of mechanical hemolysis which produces anemia in occasional Starr valve patients. Even so, the Starr valve has remained the replacement of choice.

(For further information on these procedures, refer to Baird and Lipton's excellent article.[6])

(b) *Mitral Valve*

An old, established, and widely used operation is mitral valvotomy or mitral split. In this closed heart procedure, the stenosed valve cusps are split along thei rline of adhesion with the fingers or (if it is too tightly adherent or calcified) with a mechanical dilator. In some cases of mitral insufficiency, mitral annuloplasty was performed. This simply means that the mitral ring is made smaller surgically. Therefore the procedure is not useful to a patient whose valve has been severely damaged e.g. by acute bacterial endocarditis. This pointed out the necessity for a prothesis to replace the destroyed valve in these cases.

The first attempts at replacement were with varieties of arrangements of cusps made of teflon and other materials. These have not proven to be very satisfactory. The preothesis most in use today is the *Mitral* Starr Ball-Valve[7] which is inserted into the mitral orifice. It is similar to, but large than, the aortic Starr valve. The primary complication is thrombus formation in the left atrium (along with thrombosis of the cage) with subsequent embolization. Therefore an anticoagulant regimen is required with its consequent complications. The operative risk is higher with the mitral than with the aortic Starr.[4 9 10]

To summarize, the Starr valve in the aortic orifice has proven to be a very successful operation. The mitral Starr valve, although not as safe, is still useful (especially when compared to the mortality of those patients not operated upon). The main problem with these two prostheses is the thrombotic complications requiring anticoagulants probably for life. Also, although very long term results are not yet available, preliminary reports indicate that late failure is a problem with these devices.[9 10] The prospect of poor long term survival is not encouraging. In an elderly patient, prolonging life for a few years may seem sufficient. But for a young man, long term survival is essential, and in all probability the Starr valves will not be able to provide it. Therefore there is justification in searching for new methods of valve replacement. Many prominent surgeons are now looking to tissue transplantation to solve the problem.

VALVE TRANSPLANTATION

Due to the aforementioned problems with prosthetic valve replacement, much work has been done, both in animals and in man, with valve transplants. Methods used in our lab for transplant experiments, and the results of these experiments, will be discussed. Also, data will be given from operations (performed at the Toronto General Hospital and other hospitals around the world) involving homotransplantation of human aortic valves into the aortic and mitral orifices of other humans.

1. Homograft

(a) *Removal from cadaver*

The aortic valve is removed from the cadavre under sterile conditions. With dissecting scissors, the ascending aorta is cut across just below the origin of the innominate artery. Then the scissor is inserted into the superior vena cava and a running cut is made through the right auricle close to the aorta, down thru the tricuspid orifice and across the interventricular septum (great care is required here so that the aortic cusps, which extend deep into the substance of the heart, won't be nicked). The cut is then continued up through the mitral orifice into the left atrium close to the aorta, and through the artial septum back to right atrium. The coronary arteries are now cut across close to their origins and the valve lifts out cleanly, like coring a pineapple, leaving a fairly intact heart for the pathologists.

Valves may be taken from any cadavre for which consent to autopsy has been signed. Age is no barrier. The only limitations are: 1) an overwhelming septicemia at death, and 2) aortic valve disease. There is no data on how long after death the valve may be taken and still obtain good results at operation, but it seems obvious that the sooner the better.

(b) *Sterilization*

After removal, valve is trimmed to remove all excess tissue possible and the orifice is measured with standardized Starr rings. Then it is incubated at body temperature for three hours in a solution of 1% bicarbonate-saline solution, and 9% distilled water. This sterilizes it very effectively. The valve is then removed and irrigated with sterile phosphate buffer to regain physiological pH. Next, a small piece of the valve is snipped off for use as a culture specimen, and the remainder is dropped into a sterile vacuum bottle and sealed. The valve is now freeze-dried as soon as possible.

(c) *Freeze-drying*

Freeze drying, or lyophilization, is a process which consists of rapid freezing to very low temperatures and then rapid dehydration from the frozen state by a high vacuum pump. Under low pressure, frozen water goes directly into the gaseous phase without passing through the liquid phase. All but 4% of the cell water (that 4% which is bound in chemical compounds) is evaporated out. In this dehydrated state, the valve may be stored at room temperature for an indefinite length of time since all enzymic reactions have been almost completely arrested.

(d) *Storage, Selection, and Reconstitution*

After freeze-drying, the bottle containing the valve is labelled and stored in the valve bank of the hospital which we set up this past summer. A filing card system. with cards containing full particulars including cause of death of donor and size of valve, makes selection of valves for use in patients easy and convenient. With a valve is required for surgery an estimate is made of the size of valve needed, a selection is made from the file cards, and the appropriate valve is obtained from the bank. The valve is reconstituted by the addition of sterile distilled water. The process requires thirty minutes for complete reconstitution if carried out at under normal pressure which is standard procedure now. *(If the valve is allowed to remain under low pressure the process of reconstitution is speeded up. A needle attached to a rubber hose from a bottle of distilled water is inserted through the rubber cap of the vacuum bottle containing the valve. The water is sucked in by the vacuum. Since there is, theoretically, a vacuum*

between every molecule of the valve, the water is pulled into all these spaces rapidly. The valve is completely reconstituted in thirty seconds.)

(e) *Data on human homograft operations*

1) AORTIC-TO-AORTIC TRANSPLANTS

The first successful homograft aortic valve procedure was carried out by Gordon Murray of Toronto in 1956.[11] Using closed-heart techniques, he inserted the graft into the descending thoracic aorta just distal to the origin of the left subclavian artery. These grafts have been shown to function well for periods of up to 8½ years.[12] The first aortic *valve* replacement with a homograft was carried out in Toronto in 1961. Since then, Barratt-Bayes of New Zealand.[13] Ross of London,[14] and Davies at Guy's[15] have continued with similar procedures.

i) Method of insertion into subcoronary position

The coronary orifices of the graft are sutured closed. The valve is then trimmed so that only the cusps and their attachments to the aortic wall remain. The patient's cusps are excised near their attachments and the homograft is sutured into position. Reinforcing stitches at the commisures are tied outside the aorta. This procedure is done on full cardiopulmonary bypass.

ii) Results

Eight operations performed by a Toronto group led by Murray[11] have produced 3 late deaths, with 5 patients still alive and in Class I of the New York Heart Association classification. There has been no thrombosis and no embolization. As previously mentioned, survival time has ranged up to 8½ years. Autopsies on those which died revealed soft and pliable cusps even after 8 months. The microscope showed only a slight thickening of the valve. What was of great significance was that the donor valve had fused into the structure of the recipient's aorta and there were no allergic inflammatory cells present.

Barratt-Boyes[13] reported 52 survivors of 57 operations. About one-half of these have shown some clinical evidence of insufficiency but the status of over 90% of all survivors (ranging up to 2 years) was rate was good. The cusps of the deaths showed little allergic reaction and no deterioration.

Ross[14], in a series of 12 patients, reported 2 early deaths and 2 others within 3 months. The remaining eight have survived up to 12 months and are doing well except for some insufficiency in 2. He also reports minimal evidence of an allergic reaction.

Davies[15] reports 12 out of 12 survivors up to 2½ years. Some residual insufficiency was recorded in 9 of these on cardiac catheterization and all have a murmur. Ten have maintained there initial improvement with no signs whatsoever of any progressive deterioration of the valve. There is no clinical evidence of stenosis, calcification, or allergic reaction.

Bigelow and Heimbecker are beginning a large series and early results are encouraging.

All these studies are continuing and the long-term results should prove interesting reading in the future.

2) AORTIC-TO-MITAL TRANSPLANTS

Although many of these procedures have been carried out with good results experimentally e.g. Murray,[11] Duran (British Journal of Surgery, July, 1965), and Heimbecker (not yet published), surgery in humans is still in its infancy. Heimbecker's cases[16] are the only ones yet reported. I had the good fortune to be involved in one case Dr. Bigelow performed this summer. The patient was still doing well when this was written, four weeks afterwards.

i) Method of insertion into mitral orifice[16]

Again the coronary orifices are sutured closed. The donor valve is trimmed so that it is circular proximally and scalloped distally. Thus only three long arms (to which the commisures attach) remain of the ascending aorta. The graft is placed in the mitral orifice through a left atriotomy incision, and the donor valve annulus is sutured to the patient's mitral annulus. Then long needles are used to suture the three arms of the graft to the ventricular wall individually. These sutures are brought through the wall and tied to teflon buttons on the exterior of the heart. This procedure is also done on full cardiopulmonary bypass.

ii) Results, of course, are sparse. But it is worth mentioning that in one of Dr. Heimbecker's cases the patient lived 30 days post-operatively at which time he succumbed to chest infection and electrolyte imbalance. Autopsy showed the donor cusps to be "completely normal, in good position and functioning well". The patient had had no significant murmurs post-operatively.

f) *Discussion*

1) PROBLEMS AND COMPLICATIONS WITH HOMOGRAFT VALVES

i) Allergic reaction to foreign tissue

This problem was cause for great concern at first but no serious immune reaction has been demonstrated so far. Immuno-suppressant drugs were given to earlier patients but most surgeons now fell that they are no longer required. The lack of blood flow through the valve is the principle reason for the lack of rejection. Even a normal human valve has a poor blood supply. Therefore bacterial antigens cannot easily stimulate the production of circulating antibody (e.g. in acute bacterial endocarditis), and if some antibody is produced it cannot easily get back into the valve to act against it. The grafted valve has no blood supply at all. Therefore there is even less opportunity for antibody

formation. (When the donor valve is inserted into a patient, its endothelial and cellular fibrous tissue elements are no longer alive. Only the tough elastic and collagen fibre framework remains; any cells which grow into this are the patient's own cells. It may be hard to believe that the valve is functional though metabolically inert. But Ross has shown that even a valve accidentally allowed to decompose in sterile distilled water was still working efficiently at the end of three months. The cusp structure remained pliable and the valve was competent although all the cells were gone.) Again let me say there has been minimal evidence of an immune reaction in man. There is some thickening of the cusps and some invasion of host cells, viz. fibroblasts and endothelial cells, but Davies[15] found no rond cells, no globulin deposits, and no circulating anti-valve antibody.

Heimbecker, in a soon to be published report, found some cusp edema present at 8 weeks which usually resolved by 12 weeks in dogs. There was gradual replacement of the homograft tissue by host tissue which closely ressembled normal valvular tissue. He concludes that host rejection was a factor in valve destruction in one-third of the dogs which died. There are two suggestions why there are better results in human patients. 1) The human aortic valve is less vascular than the dog cusps and 2) Heimbecker believes that many reports of valve destruction due to host rejection may have, in fact, been due to early undetected cases of bacterial endocarditis which is common in the dog due to unterile operating room conditions.

ii) Technical problems

The procedure is more difficult than the insertion of the Starr valve. This is very important since the results depend almost entirely on the technical success of the operation. 1) The homograft is very soft and pliable and therefore harder to handle than the cloth prostheses. This necessitates a longer time spent on the pump and operative risk increases accordingly. This problem will probably be solved with greater experience and newer techniques. 2) Variation in the size of the ring, prescence of calcium in the ring, and difficulty in obtaining a firm fixation of the commisures at the correct tension have lead to a greater post-operative incidence of valve insufficiency than the Starr valves. These problems will, hopefully, also be solved as experience is gained.

iii) Availability

Due to the limited number of cadavres and limited range of valve sizes, the availability of cadavre material remains one of the largest problems which must be surmounted.

2) ADVANTAGES OF VALVE HOMOGRAFTS

i) No thrombosis or embolism reported as compared to cloth protheses therefore anticoagulants are not required.

ii) Cloth valves have a tendency for late failure. So far the homografts have shown no tendency to deteriorate.[12 13 14 15]

iii) Homograft valves are much more hemodynamically acceptable than the prosthetic valves. "There is no precedent in medical history for relief that the body will passively accept foreign bodies such as cloth prostheses for a long, trouble-free period. This is particularly true with heart valves where motion is an integral part of function and is essential for moment-to-moment survival. Ball-valves, due to their bulk and central localization, impose a considerable element of turbulence and dynamic impedence to forward blood flow. They exert forward strain on the line of attachment in systole and backward strain in diastole".[17] Also related to this is the aforementioned problem of mechanical hemolysis which is non-existent with the homograft. Leaflet valves are also subject to ready detachment, flex fatigue and ultimately fracture.

These factors assme more importance in younger patients to whom long term survival is a necessity; the primary problems with the prosthetic valves are in terms of long term survival. The life expectancy of these patients averages about 2½ years which for a young man is very short. Therefore the future of the homograft valve will depend on its ability to increase the survival time of these patients. Whether it will fulfill its early promise only time will tell.

2. AUTOGRAFT

This section, and the one which follows on heterografts, review two aspects of valve replacement which are at the moment experimental, but which in the future may become standard procedures.

If a method could be found to replace a patient's valve with a valve made from his own tissues, two problems would be solved. 1) There will no longer be any problems with availability of valve grafts and 2) the possibility of host reaction to the graft will be eliminated forevermore. We are now working on autografting in our lab.

(a) *Methods*

1) Templeton and Gibbon[18] employed autograft pericardium as a sheet implanted within the heart. This became shrunken and curled with time.

2) Bailey,[17] after excising the patient's valve, peeled off tissue from inside the aorta (though the media) and shaped this hinge of tissue into valve cusps. This procedure was performed in one patient who survived 7 months and died of infection, not valve failure. The valve did well clinically but microscopic sections showed changes which could be interpreted equivocally as harmful degeneration of the valve or as beneficial reaction of the pedicle graft to unaccustomed stress.

3) At the Banting, we have been trying to make dogs *grow* their own valves. Materials such as teflon, cotton net, and loose-mesk silk are placed in lucite molds. The mold consists of 2 slabs with three bumps in the form of aortic cusps, protruding from the inside of one slab, and three corresponding depressions on the inside of the other slab. The three protrusions fit exactly into the three depressions. The mold material is slipped in between the slabs like the filling in a sandwich. The slabs have 4 holes drilled in their 4 corners through which heavy silk sutures are placed and tied tightly enough to hold the material in place, but not too tightly to prevent fibrous tissue ingrowth. The prepared mold has the size and appearance of a bar of soap. The complete mold is then sterilized and inserted at operation subcutaneously into the flank of a dog (the axilla or any other convenient subcutaneous area would be used in humans). A few weeks are allowed for fibrous tissue to grow into the mold in reaction to the foreign material. The mold is then cut out, opened, the fibrosed material removed and trimmed to surgical requirements. Later the graft is inserted into the dog's valve orifice.

There is precedent for this procedure. In 1961, Heimbecker and associates implanted teflon vessel molds in dogs. When fibrosed, these scar tubes were removed and replaced in the dog's abdominal aorta with great success.[19]

(b) *Results*

Two teflon molds were implanted one year ago for 6 weeks. On removal of the mold from one dog, it was found to be encapsulated by fibrous connective tissue, but the scar tissue had not grown into the mold itself. The other mold was found to be successfully fibrosed. This graft was inserted into the dog's tricuspid orifice with good results. This year, 2 cotton and 2 silk molds were implanted on the theory that these reactive foreign materials would produce a much stronger fibrous tissue reaction than the rather inert teflon. At the time of writing, the molds had become firmly attached in the dog's subcutaneous tissue. As they are not quite ready for removal, the validity of our theory cannot be tested as yet.

One major fear was the rejection of the mold by the body. Work on clinically implanted cardiac pacemakers has demonstrated that foreign bodies subcutaneously can be prevented from sloughing so this fear has been largely dispelled. We feel our method has good possibilities and will prove practical and effective.

3. Heterograft

One of the major problems in homograft mitral valve replacement, as already indicated, is the difficulty in obtaining donor aortic valves of a size sufficiently large to fit the patient's mitral orifice. The same difficulty arises in aortic valve replacement when the patient's aortic annulus is dilated due to primary or secondary factors. The answer may lie in heterotransplantation.

Experiments done in our lab which consisted of inserting *calf* aortic valves into the dog tricuspid orifice (rather than into the mitral area where there are more technical difficulties due to the higher pressures on the left side of the heart) have indicated that the procedure may be applicable to humans. The loudest objections would concern the possibility host rejection of the graft due to the vast species difference. But in all our dogs so far only minor evidence of rejection phenomena has been observed. Our longest survivor (4½ months), to date, succumbed to bacterial endocarditis involving the transplanted valve, but he had produced no allergic reaction to the calf graft. Polymorphs and fibroblasts (probably due to the endocarditis) had grown into the framework of the valve, but no round cell infiltration was apparent. The suture line between the donor valve and the recipient myocardium had closed so they appeared as a structural unit. I hopefully submit that the calf is closer to the dog, phylogenetically, than to the human. But the almost complete lack of serious immune reactions in calf-to-dog experiments is very encouraging. Studies are continuing.

ACKNOWLEDGEMENTS

I wish to acknowledge Dr. R. O. Heimbecker for his guidance and encouragement. Many thanks also to Dr. Colin Bryliss, Dr. R. M. Zuhoruk, Dr. E. D. Wigle, the technical staff and Miss Barbara Cruden for their patience and generosity.

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Clinical Pathological Conference

Mrs. M. B. Age: 80 yrs. Admitted Toronto Western Hospital: Aug. 19, 1963 Died: Sept. 9, 1963.

Mrs. M. B., an 80 year old widow and resident of Lambert Lodge, entered hospital August 19, 1963 complaining of diffuse severe stabbing upper abdominal pain. This had diminished since its acute onset 9 hours earlier. The pain was most severe under the right rib cage and radiated straight through to the back; it was aggravated by deep breathing. There was no previous history of abdominal pain. She became nauseated and vomited 2 cupfuls of grayish-yellow fluids 1 hour after the pain started. Vomiting had occurred 4 or 5 times subsequently yielding the same fluid.

The patient had been in Toronto Western Hospital in February 1962 with urinary incontinence. Iron deficiency anemia was discovered and occult blood in her stool ranged between 0 to 2+. X-rays of her G.I. tract and kidneys were normal. Ferrous sulfate therapy was followed by an increase in haemoglobin from 48% to 84% in 6 weeks. The patient's urinary incontinence persisted and was thought due to a large atonic bladder with overflow.

Mrs. B. stated that her weight had been stable at 190 lbs. from the previous admission. She had noted decreased appetite and "pep" over the previous several months. Constipation had become an increasing problem to her requiring more and more laxatives. She dendied any upper gastro-intestinal symptoms. Her urinary complaints of nocturnal incontinence and daytime frequency persisted. The patient had had an annual examination in Feb. 1963 at which time the liver was found to be enlarged two finger breadths below the costal margin.

The physical examination revealed an obese lady in moderate distress with a temperature of 99.8°F per os. The sclera and skin were icteric. No abnormal lymphadenopathy was present. The breasts and respiratory system were normal. Pulse was regular at 84 per minute; blood pressure 180/90 right arm lying. The aortic closure sound was louder than the pulmonary closure sound and the second heart sound was normally split. A grade 2/6 cystolic murmur was heard maximally down the left sternal border, but also at the base and apex. There was no evidence of congestive failure.

The abdominal wall was obese with an apron of adipose tissue and coarse striae over the flanks. The liver descended to 8 cm. in the right mid-clavicular line and to 10 cm. below the xiphoid. There was slight tenderness near the area of the gall bladder on deep inspiration and also in the epigastrium. The liver had a firm edge and a hard glossly nodular surface. In addition, a firm 8 - 10 cm. mass was palpable over the area of the left kidney which faded into an ill-defined left upper quadrant mass. Traube's space was dull to percussion. No friction rub was audible; bowel sounds were faint. Shifting dullness and ballottement of fluid was present. A gastric splash was heard. Rectal examination revealed diffuse tenderness but no stool. The rest of the examination was non-contributory.

On admission, plain films of the abdomen were normal. The laboratory confirmed the clinical impression of jaundice with a total bilirubin of 8.9 mg%. Other first day lab results were: serum amylase 373 units; SGOT 214; WBC—13,600 with polymorph response; serum Ca 8 mg%, serum phosphorus 2.8 mEq/1. On the second day additional reports were: C1 84 mEq/1, CO_2 combining power 35 mEq/1, Na 98 mEq/1, K 4.2 mEq/1 and serum amylase 193 units. The E.C.G. was normal. Urine was positive for bile and although negative for urobilin the first day, was trace the second day.

Clinically the patient's condition improved over the first four days. Her pain gradually dissipated and her jaundice cleared so that by the sixth day the serum bilirubin was within normal limits. Serum proteins were 7.1 gm% and serum Ca 7.6 mg% on the fourth day. A huge dilated stomach filled with fluid and almost completely obstructed to the passage of barium was present at fluoroscopy. Thereafter the patient received morning and eveneing gastric lavage with hourly feedings of milk in between, the received I.V. replacement fluid and electrolytes.

The aspirate from the stomach was dark coffee grounds fluid but soon became normal. Stools were 4+ for occult blood on three successive days. Stomach aspiration continued to yield 1500 - 200 cc. of fluid daily with only 500 - 800 cc. of oral intake getting through. The clinical and laboratory signs were satisfactory but the patient was not feeling much better. An overnight continuous gastric suction yielded 495 ml. of fluid containing 25 mEq/1 free acid and 95 mEq/1 total acid.

On the 17th hospital day, laparotomy was done in the hope of by-passing the continuing partial duodenal obstruction and adding to the diagnosis. Post-operatively she did poorly, deteriorating progressively. Four days following operation she became hypotensive and died.

DIFFERENTIAL DIAGNOSIS

Dr. J. R. Bingham

This case demonstrates the importance of trying a wide variety of clinical signs together postulating a single disease entity with its sequelae, rather than a variety of unassociated entities.

This 80 yr. old widow presented with diffuse stabbing upper abdominal pain. The stabbing nature of the pain suggests muscle spasm; the diffuseness suggests an inflammation involving the peritoneum. Radiation to the back is typical of involvement of structures on the posterior abdominal wall: the pancreas and the common bile duct. Pain aggravated by breathing is usually produced by structures that move with respiration. Further, this abdominal pain may be referred pain from extra-abdominal structures such as the pleura. The nausea and vomiting are probably reflex from the pain and inflammation; the yellow color to the fluid indicates that there is not complete pyloric obstruction. This pain seems to have improved after four days in the hospital.

This patient has a history of iron deficiency anemia occuring in February 1962. In elderly patients presenting with anemia, one must always be aware of the possibility of malignancies involving the stomach or colon. Although the X-rays proved to be negative, it is not uncommon to fail to see either a peptic ulcer or a malignancy on X-ray.

From the physical examination on admission, we have the following findings to aid in diagnosing the condition: hepatomegaly, jaundice, G.I. bleeding, ascites, gastric retention, and a mass in the LUQ.

1. *Hepatomegaly*

In Feb. 1963 the liver was found to be two finger-breadths enlarged, and at this time Aug. 1963 the edge was felt 8 cm. below the costal margin in the right mid-clavicular line. Whenever one describes enlargement of the liver: the upper border of the liver should always be described as well as the inferior one; it is probably best to describe the size in cm.'s as finger size varies, with mention made of how or where the enlargement was measured. This liver seems to have enlarged considerably in the past six months, unless one of the descriptions was inaccurate. This is not impossible to believe considering the obesity of the patient. The liver is described as having a firm edge and a hard grossly nodular surface. The most likely causes of this degree of enlargement are cirrhosis and neoplasms, either primary or secondary. Enlargement due to congestive heart failure can be dismissed as there is no other evidence to support congestive failure; enlargement due to biliary obstruction and biliary cirrhosis can be dismissed as there is no previous history of jaundice. In the two cases to be considered, the liver can be nodular. In a less obese patient, the distinction may be made by the consistency of the liver, as cirrhosis is firm, while the nodules in carcinoma are stony hard.

2. *Jaundice*

With any liver disease, understanding the detail of bile pigment metabolism and the production of jaundice is essential. Obstruction due to a stone or inflammation is usually intermittent, while that produced by a carcinoma is generally irreversible with the serum bilirubin gradually rising and the jaundice deepening. However, in some rare cases of carcinoma of the pancreas, there is edema and inflammation surrounding the carcinoma producing the obstruction, such that if the edema or inflammation is reduced, the jaundice may improve. In this patient the urine was positive for bilirubin, negative for urobilin the first day, trace the second. This indicates an obstructive jaundice. As the patient's jaundice improved, the cause of the jaundice is not likely due to carcinoma, unless there is the situation as mentioned previously. It may be important to note that the improvement of the jaundice occurred at the same time as the improvement in the patient's general condition and in her pain.

2. *G.I. Hemorrhage*

In Feb. 1962, the patient had an iron deficiency anemia with stools positive for occult blood. This may or may not be related to the present condition. Now, while in hospital, "dark coffee grounds fluid" was aspirated from the stomach; the stools were 4+ for occult blood. G.I. hemorrhage may result from a variety of possible conditions:

a. Peptic ulceration in the stomach or duodenum. A duodenal ulcer is commonly found in patients with cirrhosis.

b. Esophageal varices. Cirrhosis may result in portal hypertension, or metastatic lymphy node involvement at the porta hepatis may obstruct the portal vein. Although the spleen wasn't palpated which might indicate portal hypertension, Traube's space is dull to percussion suggesting an enlarged spleen that can't be felt.

c. Carcinoma or the esophagus, stomach or duodenum.

d. Carcinoma or the pancreas invading the stomach or duodenum.

4. *Ascites*

The production of ascites, as with the accumulation of fluid anywhere may be the result of: increased hydrostatic pressure, decreased plasma osmolarity, or blockage of lymphatics. Accumulation of peritoneal fluid may also be due to inflammation of the peritoneum or widespread carcinoma in the peritoneum. In this patient: if there is primary liver disease, ascites may be the result of portal hypertension and/or decrease in plasma proteins; ;if there is carcinoma anywhere, the ascites may be the result of widespread secondaries

throughout the peritoneum or metastatic lymphatic involvement blocking the portal vein or inferior vena cava. Paracentesis with examination of the fluid for: specific gravity, protein, bood and inflammatory or neoplastic cells would have been useful and should have been done.

5. *Gastric Retention*

Obstruction of gastric contents was demonstrated by: the gastric splash or physical examination, the fluoroscopy, and the aspiration of fluid from the stomach. This obstruction may be due to:

a. Non-malignant pyloric obstruction from a duodenal or antral ulcer.

b. Malignant obstruction due to carcinoma in the stomach near the pylorus.

The presence of free acid might favor a peptic ulcer although it doesn't rule out carcinoma. This is a rather high concentration of acid; normal basal values:

free acid 10 - 30 mEq/1
total acid 15 - 40 mEq/1.

6. *LUQ Mass*

Finally, there is this mass 8 - 10 cm. over the area of the left kidney. This mass is poorly described, but may be:

a. Neoplastic condition involving the pancreas, stomach, or para-aortic lymph nodes.

b. Inflammatory—an abscess or the pancreas or from perforation of a gastric ulcer.

c. A pancreatic cyst.

d. The spleen.

e. Fecal material or a disease process in the splenic flexure of the colon.

Reviewing the laboratory results may give us more insight into this condition:

1. Bilirubin — 8.9 mg%; urine bilirubin +ve, urobilin −ve and trace. This indicates obstructive jaundice which cleared by the sixth day.

2. Serum amylase — 373 units (normal 80 - 180). This elevated level may be found in acute pancreatitis, obstruction of the pancreatic ducts by carcinoma or a stone, or by inflammation of the pancreas following penetration of a peptic ulcer.

3. Serum Ca^{++} — 8 mg% (Normal 9 - 11). This is often reduced in pancreatitis as fat necrosis occurs. With the release of lipases from the pancreas, free fatty acids are produced from the adjacent fat precipitating the calcium. Usually the lowest value is reached about the sixth day.

Serum Phosporus 2.8 mEq/1 (Normal 1.0 - 1.5). This value seems to be abnormally elevated, although some elevation may be the result of parathyroid action on bone salts as compensation for the low serum Calcium.

4. W.B.C. — 13,600 with polymorph response is in keeping with some inflammatory condition either due to bacterial infection or peritoneal irritation due to perforated gastric contents or released pancreatic enzymes. This is probably related to the abdominal pain experienced on admission.

5. The electrolyte values indicate a hypochloremic alkalosis probably resulting from the vomiting. It seems doubtful that a serum Na level of 98 mEq/1 is a true value. We have no indication that there is any plasma dilution, and this much Na is not lost with the amount of vomiting indicated.

6. SGOT 214 units (Normal 5 - 40). This elevation of SGOT can be found with cirrhosis or with liver neoplasms (primary or metastatic). The serum protein level of 7.1 gm% is normal and would tend to rule out chronic liver disease, although serum albumin and the A/C ratio is more useful than the total serum proteins.

With this variety of signs and lab results, is there any basic lesion which may be able to explain all the results?

—Cirrhosis with a duodenal ulcer which has perforated into the pancreas may produce many of these findings. But the jaundice is not that of cirrhosis, and there are not the other clinical signs associated with cirrhosis.

—Acute pancreatitis may explain many of the findings—the jaundice and the lab results—but not all.

—Carcinoma of the pancreas with adjacent inflammation will explain the jaundice and the lab results; if the carcinoma has spread to involve the liver and hilar nodes, and extended into the duodenum or stomach this may explain the hepatomegaly, G.I. bleeding, gastric retention and ascites.

—Carcinoma of the stomach with metastases to the liver and with extension into the pancreas with some resulting pancreatitis will similarly explain the findings.

It is unfortunate that X-ray has not aided the diagnosis. The last two possibilities are most likely. Considering the carcinoma of the pancreas; if the neoplastic condition has become so extensive as to invade the stomach or duodenum it is surprising that it has not produced more jaundice. With the previous history of iron deficiency anemia and G.I. bleeding, one wonders whether there was an early carcinoma of the stomach that went undetected.

Clinical Diagnosis

1) Carcinoma of the stomach, with metastases to the liver.

2) Carcinomatous Invasion into the pancreas with resulting acute pancreatitis.

PATHOLOGICAL DISCUSSION

DR. F. A. JAFFE

The autopsy revealed an extensive disease process. The body was that of a white, elderly adult woman with marked generalized obesity and a recent healing surgical incision to the left of the midline of the abdomen. The peritoneal cavity contained approximately 400 cc. of serous fluid. There were small deposits of fibrinous material over some areas of peritoneum and multiple nodular deposits of tumour up to 0.5 cm in diameter over the diaphragm and anterior abdominal wall, and greater omentum. Some of these latter nodules appeared to be lymphatic spread.

Stomach was greatly dilated. Over the mid-portion of the greater curvature was an area adjacent to a large abscess cavity. At this area there were two focal ulcerations. There was an irregular ulcer with firm, slightly raised, rolled margins, 1.5 cm in dia. at the pylorus. The wall of the stomach was greatly thickened; microscopic sections revealed a pleomorphic undifferentiated adenocarcinoma extending through all layers of the stomach wall and into the surrounding adipose tissue. (Fig. 1.)

Pancreas was in the usual position, 20 cm. long. Superior to the pancreas was a large area of complete necrosis of fatty tissue with abscess formation. The large abscess 12 cm long and 6 cm in diameter was adjacent to the greater curvature of the stomach and contained multiple white lobules of necrotic fat and a pale, slightly greenish-yellow pus. Microscopic sections showed: ducts filled with inspissated secretions in the tail of the pancreas; extensive fat necrosis adjacent and throughout the pancreas which had gone on to large abscess formation; the head of the pancreas almost entirely replaced by carcinoma. Carcinoma was present in nearby lymphatics and adipose tissue, and had almost occluded the postal vein by a mass of tumour growing into the lumen from the wall. (Fig. 2).

Liver weighed 2750 gm and had an unusual configuration extending far to the left. The surface was finely nodular with the appearance of typical portal cirrhosis. Sections revealed many scattered nodules of secondary carcinoma. Microscopic sections showed a network of fibrous tissue trabeculae involving both portal and central vein areas dividing the parenchyma into small nodules. Within these, the parenchyma was compressed and distorted and exhibited moderately severe patchy fatty change. In some sections, there was widespread replacement by a very pleomorphic anaplastic adenocarcinoma exhibiting extensive necrosis. (Fig. 3).

Gall bladder was small and contracted, half embedded in the liver and a tumour mass. There were several fragments of mixed stones but none in the common bile duct. The cystic duct was completely occluded by tumour; the common bile duct was compressed but not obstructed by tumour nodules.

Fig. 1. Gross section of stomach revealing thickened wall of stomach; the pyloric ulcer; pancreas with fat necrosis and areas of calcification; abscess.

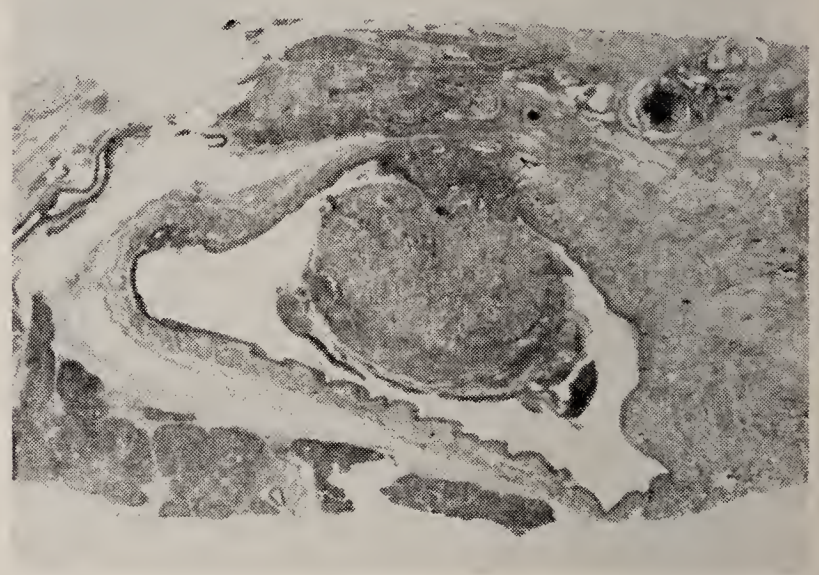

Fig. 2. Portal vein invaded and partially occluded by carcinoma.

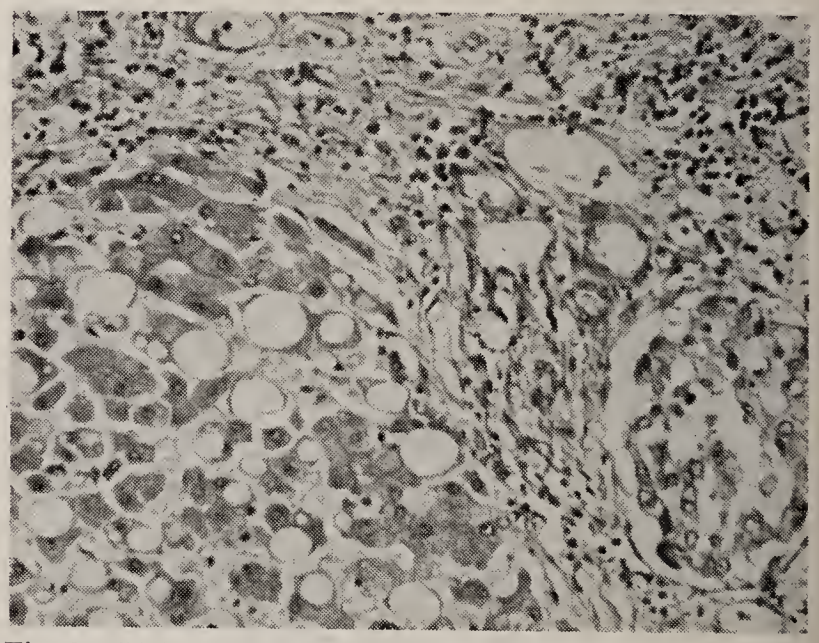

Fig. 3. H & E section of liver—fatty degeneration of liver cells with early cirrhosis; metastatic carcinoma.

Spleen weighed 450 gms (normal 150 gm) and had normal pulp.

Other microscopic sections demonstrated tumour in:

—lesser omentum, lymph nodes of porta hepatis, lymph nodes adjacent to the pancreas.

—retroperitoneal lymph nodes around the lower half of the abdominal aorta.

—peritoneal surface and lymphatics of the small intestine mesentery.

—wall of the small intestine.

—adrenal glands.

PATHOLOGICAL DIAGNOSIS

Adenocarcinoma of the stomach.
Acute pancreatitis with extensive fat necrosis.
Peritoneal carcinomatosis.
Cirrhosis of the liver.

DISCUSSION

This is an interesting case, in that many of the possibilities discussed were in fact actualities. The ascites for example could be the result of all three: carcinomatosis, portal vein obstruction by metastatic carcinoma in lympph nodes of the porta hepatis, and cirrhosis. One important point should be remembered; iron deficiency anemia in an elderly patient with some G.I. hemorrhage should never be disregarded. It may be an early sign of some malignancy which produces other symptoms only later, when it is impossible to control.

ACKNOWLEDGEMENT

I would like to thank Dr. Bingham and Dr. Jaffe for their time to make this presentation possible.

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Gaspard-Laurent Bayle

"This, the most common species of all, found in the lung, is often simple. The lungs then present tubercles, either encysted or not encysted. The tubercles vary in size from a millet seed to that of an chestnut. Miliary tubercles are commonly excessively numerous. As to the others, they are so much the fewer the larger they are, and sometimes two or three only are found."

The above is an excerpt from Gaspard-Laurent Bayle's "Researches on Pulmonary Phthisis", published in 1810. It was an outstanding clinical-pathological contribution and greatly influenced the physicians of the time, particularly Bayle's friend and colleague Laennec.

Bayle, who gave the best description of his time of the varieties of tubercular infection was born in the mountain village of Vernet in France. At a very young age he became interested in biology, but plagued with indecision, he ventured first into theology, then law, then medicine. After stormy undergraduate years Bayle was granted the degree of doctor of medicine in Paris in 1801. His late matriculation in medicine was outbalanced by his industry and talents in teaching on the wards and in the morgue and in clinical management of internal diseases. In 1807 he was appointed to the staff of Charité and the following year to the royal household and royal infimary.

Bayle revolutionized thinking concerning tubercular diseases. He taught correctly that tuberculosis was a specific disease entity and not a morbid process degenerated or descended from a preceding malady. He observed that tubercles might develop before symptoms appeared, recognized cavity formation as a complication of pulmonary consumption, and described several forms of tubercular infection. These included acute miliary tuberculosis, tubercular laryngitis, lymphadenitis, enteritis, and tuberculosis of the ovaries. His monograph which was published first in French, was translated in 1815 by Barrow of Liverpool. The preface reads as follows:

"The generic character of Phthisis may be drawn from the symptoms, or from the nature and seat of the disorder.

It is evidently necessary to unite the two characters of which we have been speaking. In fact the cough, wasting, hectic fever, and purulent expectoration, are the effects of the disorganization of the lungs. These symptoms shew that this disorganization is advanced; but the disease is no less real in its commencement, and the essential character is even then applicable. Besides, this disease may exist without presenting the union of symptoms named "Pathognomonic". Authors have remarked that different persons have died of Phthisis, who have never shewn manifest signs of it; thus persons have been seen to die, who were in a state of hectic fever and marasmus, without cough or expectoration, where numberless tubercles were found in the lungs, and what is more inconceivable, large ulcers. The same injury of the lungs has been found in other persons, of whom some appear to have had only excessive diarrhoea, and to have died of inanition alone."

The large number of dissections performed by Bayle as a staff physician at Hospital de la Charité and as a member of the Society of the Faculty of Medicine of Paris provided the protocols for a remarkable variety of tubercular cases. Each account of a case presented a clinical resume, the gross postmortem findings, and a summary of reflections. Bayle's descriptions of tubercles of the bladder, mesentery, and intestines have been chosen for excerpting.

"The bladder adhered very intimately to the anterior surface of the womb. Its internal membrane had a deep brown red colour; it was covered with tubercles pretty much crowded together, of a miliary or lenticular size, and whitish internally.

REFLECTIONS: We see that this girl died in an attack of intermittent fever. The pains she perceived in the belly proceeded from the disease of the ovarium, or of the peritonaeum, or its duplications. It is astonishing that there should be no pain in the bladder, which, as we have seen, was so much injured.

The exterior of the body presented the "embonpoint" and freshness of youth; ;the lungs were free, voluminous, hard like liver in their whole extent, and contained heavy and large tubercular masses not encysted, most of them of the size of small walnuts, others of the size of nuts, and some smaller . . . but there were in the mesentery, glands nearly tubercular throughout, and as large as almonds.

Ulcerations of the intestines are very frequent in putrid and in malignant fevers: they render the disorder more serious, but do not prevent the cure of it; and when these fevers do not terminate fatally, the ulcerations cicatrise."

Bayle died in 1816 at the early age of 42, a victim of tuberculosis, the disease that had attracted his deep interest and analytical mind.

D. A. Dellandrea, B.Sc., 6T6

ACKNOWLEDGEMENT

With this final issue of the Journal, I would like to thank Miss Janet Miller and Miss Carol Pepper for their excellent secretarial assistance in the preparation of these articles.

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On Inspection Answers

1. a. Note narrowing of the joint space with increased density of adjacent bony structures and marked hypertrophic bone formation at its edges.
   b. Diagnosis—Chronic osteoarthritis
   c.

Rheumatoid Arthritis	Osteoarthritis
More common in female	No sex predisposition
Generally under 40 years	Generally over 40 years
Inflammatory lesion of synovial membranes	Degenerative condition of cartilage and bone
Symptoms—fever, weight loss, anemia, low BMR	No constitutional disturbances
Clinical Signs	
Local signs of inflammation	No local inflammation
Marked deformity	Deformity not marked
Extreme muscle atrophy	Only disuse atrophy
Swelling of soft parts	Soft parts not swollen
Subcutaneous nodules	Heberden's nodes
Fibrous or bony ankylosis	No true ankylosis
Marked pain	Little or no pain
Complete crippling in 10%	Complete crippling rare
Radiologic Signs	
Narrowing of joint space	Narrowing of joint space
No Joint mice	Joint mice
Subluxation common	Subluxation uncommon
No spur formation	Marginal bony spurs
Osteoporosis of neighbouring bone	Eburnation of subchondral bone
Marginal erosions	No marginal erosions

2. a. Diagnosis—Multiple Myeloma
   Note typical mottled appearance of skull due to diffuse punched-out osteolytic lesions.
   b. Clinical Picture

The Tumor

1) Age—usually over 40
2) Sex—more frequent in male
3) Location
   —primarily in flat bones of axial skeleton
   —almost all bones eventually involved
4) Anemia—due to replacement of marrow
5) Bleeding from mucous membranes—thrombocytopenia produced by marrow replacement

Serum Proteins

1) Inversion of A-G ratio
2) Large amounts of abnormal globulins are produced by myeloma cells — 5% are cryoglobulins
3) Copious excretion of Bence-Jones protein
   a) Small molecular weight—found in urine, not serum
   b) Present in 50% of cases of multiple myeloma (also found in leukemia and in secondary carcinoma of bone sometimes)
4) Electrophoretic pattern abnormal and specific for each patient
5) Red cell rouleux and elevated ESR due to coating of red cells with abnormal globulins
6) Decreased antibody production (since abnormal globulins produce at expense of normal) —susceptible to infection
7) Amyloidosis occurs in 25% of cases

Kidney

1) Renal function is impaired — may lead to uremia and death
2) Tubules filled with abnormal protein casts often surrounded by giant cells (Bence-Jones casts)
3) Metastatic calcification (nephrocalcinosis) due to osteolysis with release of calcium
4) never get hypertension

3. a. Diagnosis—Carcinoma of the prostate with widespread osteoblastic metastases in spine, pelvis, ribs and femora. Osteolytic lesions are also present.

   b. Further procedures are:

   1. Renal function tests
   2. I.V.P. (if renal function is adequate) shows condition of the kidneys, ureters and bladder. This procedure is also used to show residual urine rather than a retrograde cystogram requires insertion of a catheter with the consequent risk of introducing infection.
   3. Needle biopsy.

   c. Page 854, Christopher's Textbook of Surgery

ANATOMIC LOCATION	CONGENITAL TYPES	ACQUIRED TYPES
Lower tract		
Urethral	Congenital phimosis Atresia Stricture (meatus) Diverticulum Abnormal openings and anomalies	Acquired phimosis Stricture Stone Tumor Fistula Divertculum
Urethrovesical	Posterior urethral valves Hypertrophied verumontanum Contracture of the neck Hypertrophy of the neck	Prostatism Cysts Hyperplasia Cancer Contracture or median bar
Vesical	Anomalies Congenital diverticulum Abnormal muscle Neurogenic bladder	Tumor Diverticulum Stone Neurogenic bladder

Upper tract		
Ureteral	Valves Strictures Ureterocele Ectopic ureteral orifice	Ureterovesical conditions Stone, blood, clots, etc. Tumor Strictures, ureteritis and periureteritis Seminal vesiculitis Pregnancy Pressure (extraureteral)
Pelvic and renal	Ureteropelvic junction Anomalous vessels High insertion Congenital stenosis	Ureteropelvic conditions Pelvic and caliceal Stone Tumor Ptosis Stricture

4. a. The primary disease is idiopathic ulcerative colitis.
   b. The superimposed lesion is carcinoma of the colon.
   Note the typical apple-core appearance of the lesion due to annular type constriction.
   Patients with ulcerative colitis have a 50 times greater chance of developing this complication than the general population.
   c. Types of Intestinal Obstruction

I Mechanical

A. Intraluminal—these are rare
   1) Gall stone 2) Fecalith impaction
   3) Mass of ascaris 4) Polypoid tumor
   5) Foreign body

B. Intrumaral — usually chronic obstruction which may become acute
   1) Neoplasm — either projecting into or constricting lumen
   2) Inflammation—regional ileitis or TB
   3) Strictures
      (a) congesital atresia or stenosis
      (b) acquired — inflammatory or traumatic

C. Compression from without
   1) Strangulated hernia
   2) Fibrous bands or adhesions producing kinking (inflammatory, traumatic or congenital)
   3) Volvulus
   4) Intussusception
   5) Pressure from enlarged nodes, tumor, or blood vessel

II Functional (Ileus)

A. Paralytic (adynamic)—reflex paralysis of bowel
   1) Peritonis
   2) Inflammation of a segment of bowel-peristaltic wave can't pass segment (may reflexly involve whole bowel)
   3) Superior mesenteric artery or vein occlusion. Variant of 2. Occlusion produces gangrene and inflammation.
   4) Electrolyte imbalance—especially potassium deficiency
   5) Reflexly due to remote causes e.g. pneumonia (especially in children), trauma, burns, surgical operations, septicemia

B. Spastic (dynamic)—uncommon

5. a. Abnormal Findings
   1. Fine ragged outline to the bowel from the mid-transverse colon to rectum denoting ulceration (saw-toothing).
   2. Gradual narrowing in the transverse colon and tubular narrowing throughout the rest of the colon.
   3. The rectal ampulla never fills out in a normal fashion.
   4. Loss of haustration in distal colon (cf. Proximal colon)
   5. Distal colon is shortened indicating fibrosis.

   b. Diagnosis—Idiopathic ulcerative colitis.

   c. Complications

I Local

A. Perianal abscesses
B. Fistulae-in-Ano
C. Rectal strictures
D. Perforation
E. Localized peritonitis
F. Pseudo polyposis
G. Carcinomatous changes

II Systemic

A. Arthritis
   1—Large joints
   2—Spine also in male

B. Skin
   1—Erythema nodosum
   2—Erythema multiformae
   3—Pyoderma gangrenosum

C. Eyes
   1—Choreoretinilis
   2—Iridocyclitis

D. Migratory thrombophlebitis

E. Endocrine abnormality, especially amennorhea.

F. Amyloid Disease

G. Possibly
   1—Cirrhosis of liver
   2—Pancreatic fibrosis

6. a. The procedure is a coeliac arteriogram. It is a relatively new procedure which is just now coming into prominence as a valuable aid in diagnosis. Frequently it is the only method of making a positive diagnosis in the many lesions arising in this area which are difficult to diagnosis early, either clinically or in the lab.

The radiologist makes a percutaneous stab of the femoral artery, then threads a radiopaque catheter up the aorta. Aided by image intensification he visualizes the catheter on a television screen and carefully guides its tip into the mouth of the coeliac artery. Then radiopaque dye is injected through the catheter into the artery and serial films are obtained at speeds of 4 per second. If properly done, the vessels in the distribution of the coeliac axis are clearly demonstrated. Injection of the superior mesentric artery is usually done simultaneously thereby adding to the efficiency of the procedure and to the accuracy of the results. Also late films in the series will demonstrate blood returning via the portal and splenic venous systems.

Some lesions which may be accurately diagnosed by this procedure are:

1) Arterial lesions
   Stenosis-intestinal angina or malabsorption
   Thrombosis-infarction
   Aneurysm
2) Spleen
   Enlargement
   Infarction
   Rupture
3) Cirrhosis of the Liver
4) Malignant tumors of Liver and Pancreas

That those are often impossible to diagnose clinically until late in their course is well known. Features which are seen on coeliac-superior mesenteric arteriography are:

a) A mass displacing vessels
b) Abnormal tumor vessels
c) A tumor blush

b. Vessels

1) Coeliac axis
2) Splenic artery
3) Hepatic artery
4) Left gastroepiploic artery
5) Right hepatic artery
6) Left hepatic artery
7) Gastroduodenal artery
8) Anterior pancreatic arcade
9) Right gastroepiploic artery
10) Posterior pancreatic arcade
11) Common inferior pancreatico-duodenal artery
12) Radiopaque catheter
13) Pancreatic branches of splenic
14) Splenic branches of splenic

7. a. Diagnosis—Esophageal and gastric varices. Note the typical worm-like appearance of these varices on barium examination.

b. Classification of liver cirrhosis—

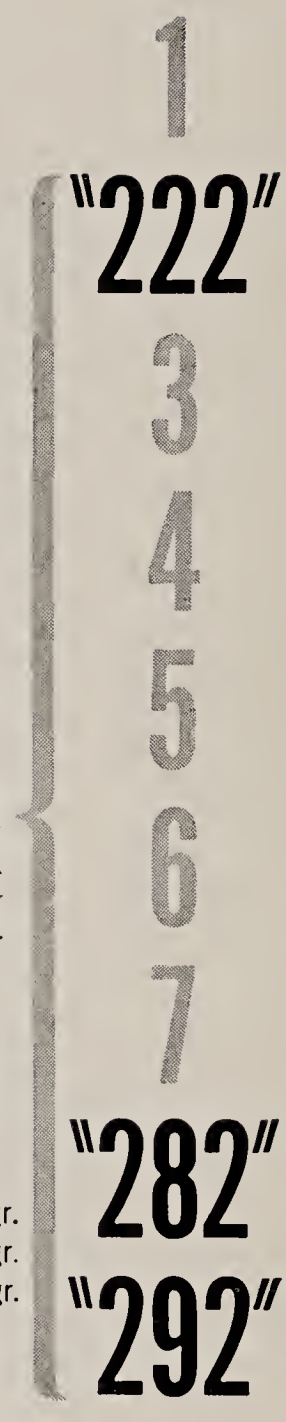
I Portal (Laennec's, alcoholic, nutritional)
II Post-hepatitic
III Post-necrotic
IV Biliary
   A. Extra-hepatic due to prolonged occlusion of major bile ducts.
   B. Intra-hepatic
      1—Primary - idiopathic
      2—Secondary - drug sensitization reaction (e.g. neo-arsenimine chlorpromazine)
V Cardiac
VI Hemochromatosis and hemosiderosis
VII Hepatolenticular degeneration (Wilson's Disease)
VIII Granulomatous—
   A. Syphylis
   B. Sarcoidosis
   C. Brucellosis
IX Metabolic—
   A. Diabetes Mellitus
   B. Hyperthyroidism
   C. Galactosemia
   D. Von Gierke's Disease
   E. Toni-Fanconi Syndrome
X Erythroblastosis fetalis.

8. a. The radial epiphysis has slipped posteriorly and laterally and is tilted backwards so that its articular surface points downwards and backwards. The ulnar styloid is also fractured.

b. Dinner-fork deformity. There is a dorsal depression in the lower one-third of the forearm above the fracture, but immediately below there is a marked prominence caused by the lower fragment having been displaced backwards carrying with it the whole of the carpus and hand. Anteriorly there is a fullness where the soft tissues are stretched over the forward-projecting upper fragment.

c. Diagnosis — Fracture-separation of the lower radial epiphysis. This is *not* a Colles' fracture. The fracture lines is through the radial epiphyseal plate (therefore, cannot be visualized) and not through the lower end of the shaft of the radius. In light of the patient's age, you should have been aware of this fact.

d. Treatment — Displacement should be corrected by manipulation under anaesthesia and a plaster applied for three to four weeks. No operation is necessary even if perfect reduction is not obtained by manipulation since the deformity is rapidly corrected by the remodelling that occurs with growth.



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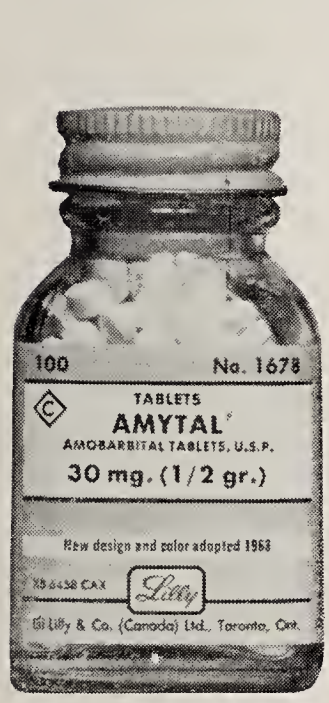

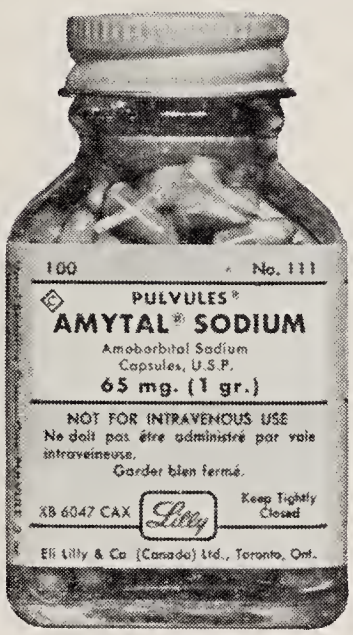

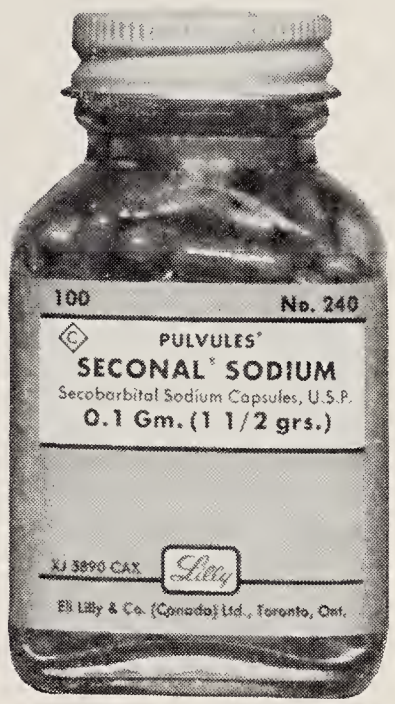

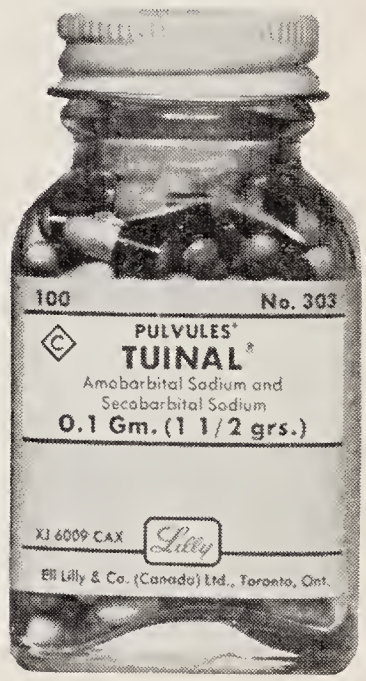

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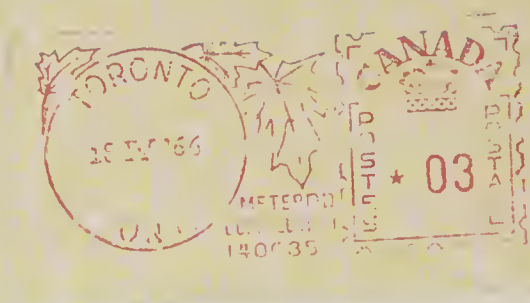

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